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TITLE: Automated Neuropsychological Assessment Metrics Version 4 (ANAM4): Select Psychometric Properties and Administration Procedures

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14. ABSTRACT

The ability to accurately and efficiently monitor the neurocognitive status of US warfighters under diverse operational and experimental conditions is of critical importance to the ongoing mission and network-centered initiatives of the United States military. The Automated Neuropsychological Assessment Metrics (ANAM) is a computer assisted tool for evaluating neurocognitive performance with demonstrated effectiveness for application in diverse military operational and research testing scenarios. The primary objective of this project is to examine select psychometric and administration properties of the ANAM4. Four studies are proposed that will 1) examine common use practices and determine the effect of specific administration procedures on ANAM4 performance, 2) assess the test-retest reliability of individual ANAM4 tests, 3) examine the validity of the ANAM4 mood scale, and 4) develop a representative normative dataset for Army National Guard service members. Data collection is complete for Studies 1, 2 and 3; data analysis and manuscript preparation is underway for all three studies. Data collection is ongoing for Study 4.

15. SUBJECT TERMS
ANAM, neurobehavioral, assessment, psychometrics, validity, reliability, normative

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INTRODUCTION

The ability to accurately and efficiently monitor neurocognitive status of U.S. warfighters under diverse operational and experimental conditions is of critical importance to the ongoing mission and network-centered initiatives of the U.S. military. The Automated Neuropsychological Assessment Metrics Version 4 (ANAM4) is a computer-assisted tool for evaluating neurocognitive performance with demonstrated efficacy for application in diverse military operational and research testing scenarios. The primary objective of this multi-study project is to examine select psychometric and administration properties of the ANAM4. This project includes four studies that will i) examine common use practices and determine the effect of specific administration procedures on ANAM4 performance (Study 1), ii) assess the test-retest reliability of individual ANAM4 tests (Study 2), iii) examine the validity of the ANAM4 mood scale (Study 3), and iv) develop a representative normative dataset for Army National Guard Service members (Study 4).

Body

This project was funded 01 December 2007. The approved study timeline/SOW is presented in **Table 1.**

Table 1: Statement of Work/Study Timeline (Original, 2007)

Year 1	**Months 1-2**	**Task 1**	Plan and finalize logistics for Phase I (Studies 1-3)
	Months 3-12 (Dec 2008)	**Task 2**	Subject recruitment, data collection and data management for Studies 1-3
Year 2	**Month 13-14**	**Task 3**	Perform preliminary data analyses for Study 3
	Month 15-24 (Dec 2009)	**Task 4**	Complete data collection for Study 1
		Task 5	Perform preliminary data analyses for Study 1
		Task 6	Continue recruitment, data collection and data management for Study 2 & 3
		Task 7	Complete data collection for Study 3
Year 3	**Month 25-36 (Dec 2010)**	**Task 8**	Complete data collection for Study 2
		Task 9	Plan and finalize logistics for Phase II (modified Study 4)
		Task 10	Complete data analyses for Studies 1, 2, 3
		Task 11	Preparation of journal manuscript(s) for Studies 1, 2, 3
		Task 12	Preparation of Project report for Studies 1, 2, 3
		Task 13	Set-up data management procedures for Study 4
Year 4	**Month 37-48 (Dec 2011)**	**Task 14**	Initiate data collection procedures for Study 4
		Task 15	Carry out data collection procedures for Study 4
		Task 16	Initiate integrative data management structure set up for Study 4
		Task 17	Operationalize database for Study 4 analysis scheme
		Task 18	Perform preliminary data analyses for Study 4
		Task 19	Complete data collection procedures for Study 4
Year 5	**Month 49-60 (Dec 2012)**	**Task 20**	Complete data analyses for Study 4
		Task 21	Prepare Study 4 manuscript(s) for peer review
		Task 22	Preparation of Project Final Report

A request for a 12 month no-cost extension for this study was approved on 7 November 2012, extending study activities through December 2013. A modified statement of work, approved as part of the no-cost extension, is presented in **Table 6**.

Table 6: MODIFIED SOW for remaining PROJECT Tasks and STUDY TIMETABLE (Nov 2012)

Year 4	**Month 37-48 (ending Dec 2011)**	**Task 14**	Initiate data collection procedures for Study 4
		Task 15	Carry out data collection procedures for Study 4
		Task 16	Initiate integrative data management structure set up for Study 4
		Task 17	Operationalize database for Study 4 analysis scheme
Year 5	**Month 49-60 (ending Dec 2012)**	**Task 18**	Conduct data collection procedures for Study 4 (cont'd)
		Task 19	Complete manuscript preparations/submissions for Studies 1-3
		Task 20	Set up/operationalize data analyses plan for Study 4
Year 6	**Month 61-72 (ending Dec 2013)**	**Task 21**	Complete data collection for Study 4
		Task 22	Complete data analyses for Study 4
		Task 23	Prepare Study 4 manuscript(s) for peer review
		Task 24	Preparation of Project Final Report

A request for an additional 12 month no-cost extension for this study was approved on 25 September 2013, extending study activities through December 2014. The modified statement of work is presented in **Table 7**.

Table 7. MODIFIED SOW for remaining PROJECT Tasks and STUDY TIMETABLE (Nov 2013)

Year 5	**Month 49-60 (ending Dec 2012)**	**Task 18**	Conduct data collection procedures for Study 4 (cont'd)
		Task 19	Continue manuscript preparations/submissions for Studies 1-3
		Task 20	Set up/operationalize data analyses plan for Study 4
Year 6	**Month 61-72 (ending Dec 2013)**	**Task 21**	Continue data collection for Study 4
		Task 22	Continue manuscript preparations/submissions for Studies 1-3
Year 7	Month 73-84 (ending Dec 2014)	**Task 23**	Complete data collection for Study 4
		Task 24	Complete data analyses for Study 4
		Task 25	Complete manuscript preparations/submissions for Studies 1-3
		Task 26	Prepare Study 4 manuscript(s) for peer review
		Task 27	Preparation of Project Final Report

Task 1 (Month 1-2)
Plan and finalize logistics for Phase I (Studies 1-3) – COMPLETED
All logistical aspects for HURC approved studies (Studies 1-3) have been confirmed. Recruitment procedures, equipment, testing facilities, and other data collection elements have been finalized and are now complete

Task 2 (Month 3-12) Subject recruitment logistics, data collection and data management for Studies 1-3 – COMPLETED
Subject recruitment, data collection and data management efforts have been completed for Studies 1-3. Recruitment of both Human Research Volunteers and Civilians was effective and efficient.

Task 3 (Month 15-24) Perform preliminary data analyses for Study 3– COMPLETED
All preliminary data analyses for Study 3 have been completed. Initial analyses suggested that additional participants would be necessary to explore noted differences between military and civilian participants on discrete on mood measures. Thus an amendment (#4, 14 July 2009) to increase enrollment from 50 to 80 participants was submitted and approved. Higher-level analyses are nearing completion on this expanded sample.

Task 4 (Month 15-24) Complete data collection for Study 1– COMPLETED
Study 1 involves the examination of common use practices and specific administration procedures (individual or group administration, practice or no practice, single session or two sessions) on ANAM4 task performances. Our recruitment goal for Study 1 was 90 participants, 30 participants per condition. Enrollment data are presented in **Table 2**.

Table 2. Study 1 Enrollment

# Participants Enrolled	90
# Participants Completed	86*

**NOTE: 15 participants completed the ANAM4 without practice test modules; 15 participants completed the ANAM4 in a group setting and 15 participants completed the ANAM4 in two administration sessions. The remaining 41 participants served as controls for these discrete administration scenarios (individual administration using practice test modules and completed in a single testing session). Thus each condition had at least 30 participants, as required.*

Task 5 (Month 15-24) Perform preliminary data analyses for Study 1 – COMPLETED
Preliminary analyses (sample characterization and demographic analyses) on the Study 1 data set have been completed.

Task 6 (Months 15-24) Subject recruitment, data collection and data management for Studies 2 & 3 – COMPLETED
Our recruitment goal for Study 2 was 90 participants, 30 participants per condition (days 1 & 7 / days 1 & 30 / 7 consecutive day retest). Recruitment goal for Study 3 was 80 participants. Recruitment goals were reached for Studies 2 and 3 and data collection has been completed for these studies.

Task 7 (Months 15-24) Complete data collection for Study 3 – COMPLETED
Data collection for Study 3 is complete. Enrollment data are presented in **Table 3**.

Table 3. Study 3 Enrollment

# Participants Enrolled	113
# Participants Completed	77

Task 8 (Months 25-36) Complete data collection for Study 2- COMPLETED
Data collection for Study 2 is complete. Enrollment data are presented in **Table 4**.

Table 4. Study 2 Enrollment

# Participants Enrolled	99
# Participants Completed	92

Task 9 (Months 25-36) Plan and finalize logistics for Phase II (modified Study 4) – COMPLETED

The Study 4 protocol has been reviewed and approved by USARIEM HURC and HRPO (final approval to initiate received June 2011). Endorsement of the study by the National Guard Bureau (NGB) was received 20 October 2011 and all 8 states (Arizona, Kentucky, Maine, Minnesota, Mississippi, Montana, Oklahoma, Pennsylvania) have been contacted by both NGB and study staff. Oklahoma declined participation in September 2012. We identified Texas as a suitable replacement for Oklahoma and secured NGB endorsement for the state in October 2012.

Task 10 (Months 25-36) Complete data analyses for Studies 1, 2, 3 - IN PROGRESS
Preliminary data analyses have been completed for each of the studies. We are currently conducting higher-level analyses for data within each of these studies.

Task 11 (Months 25-36) Preparation of journal manuscript(s) for Studies 1, 2, 3 – IN PROGRESS
Manuscripts for each of these studies are in draft form and are waiting for completion of higher-level analyses to finalize and submit to peer-reviewed journals.

Task 12 (Months 25-36) Preparation of project report for Studies 1, 2, 3 – COMPLETED
Project summaries and completion of Studies 1-3 were included in previous continuing review reports. Manuscripts for these studies are in progress.

Task 13 (Months 25-36) Set-up data management procedures for Study 4 - COMPLETED
All procedures involving data management have been established. Study datasets have been created and are being populated as data are obtained from field sites. Data entry and checking have been successfully coordinated.

Task 14 (25-36) Initiate data collection procedures for Study 4 – COMPLETED
Data collection procedures were initiated in Arizona, Montana and Maine in the prior reporting period (2012). Planning activities for data collection trips to Minnesota and Kentucky were initiated during this reporting period, with initial data collection trips completed in August (MN) and October (KY) of this period, respectively.

Task 15 (37-48) Carry out data collection procedures for Study 4 – IN PROGRESS
Data collection was completed in three states during this reporting period: Arizona (one trip in this reporting period, completed March 2013), Maine (five trips in this reporting period, final trip in June 2013), and Montana (3 trips in this reporting period, final trip in February 2013) Data collection was initiated in Minnesota and two trips have been completed during this reporting period (August 2013). Data collection also was initiated in Kentucky, with one trip completed (October 2013) during the current reporting period.

Current enrollment by state is presented in **Table 5**.

Table 5: Current Study 4 enrollment

State	# Completed

Arizona	223
Maine	250
Montana	301
Minnesota	185
Kentucky	34
Total	**993**

Task 16 (37-48) Initiate integrative data management structure set up for Study 4 - COMPLETED
Databases associated with Study 4 have been created and are being populated as data are obtained and cleaned.

Task 17 (37-48) Operationalize database for Study 4 analysis scheme – COMPLETED
Data entry has commenced and databases continue to be refined for analytic schemes.

Task 18 (37-48) Conduct data collection procedures for Study 4 (cont'd) – IN PROGRESS
Data collection procedures have been completed in three states (AZ, ME, MT) and are ongoing in two states (KY, MN). We are currently coordinating approvals with three states (Mississippi, Pennsylvania and Texas).

Task 19 (49-60) Complete manuscript preparations/submissions for Studies 1-3- IN PROGRESS
We have completed primary data analyses for Studies 1-3. A manuscript is near completion for Study 3, with manuscripts in preparation for Studies 1 and 2.

Task 20 (49-60) Set up/operationalize data analyses plan for Study 4 **– In PROGRESS**
The primary data analytic plan for Study 4 has been completed.

Task 21 (49-60) Continue data collection for Study 4 – IN PROGRESS
Data collection is ongoing in two states (KY, MN). We are currently coordinating approvals with three states (Mississippi, Pennsylvania and Texas).

Task 22 (49-60) Continue manuscript preparations/submissions for Studies 1-3 – IN PROGRESS
A manuscript is near completion for Study 3, with manuscripts in preparation for Studies 1 and 2

Task 23 (61-72) Complete data collection for Study 4 - PENDING

Task 24 (61-72) Complete data analyses for Study 4 - PENDING

Task 25 (61-72) Complete manuscript preparations/submissions for Studies 1-3 - PENDING

<u>Task 26 (61-72)</u> Prepare Study 4 manuscript(s) for peer review - PENDING

<u>Task 27 (73-84)</u> Preparation of Project Final Report - PENDING

KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments during the current study period include:

- Progress on key tasks (Study 4 data collection, Study 1-3 data analyses and manuscript preparation) was delayed due to furlough and the government shutdown.

- Higher-order analyses are underway for Studies 1 & 2. Manuscript preparation is underway for Studies 1-3, with Study 3 manuscript near completion.

- Continuing Review report was reviewed and approved by the USARIEM HURC (25 March 2013).

- Five out of eight states have agreed to participate in Study 4 data collection and provided TAG-level approval; approvals are pending (expected) in two additional states and under consideration in a third.
    - During this reporting period, data collection activities were carried out in 5 states (AZ, KY, ME, MN, MT) and completed in three (AZ, ME, MT).

- A 12 month no-cost extension for this study was approved on 25 September 2013, extending study activities through December 2014.

- In a separate research project (USARIEM #11-07HC; PI: Proctor), we have obtained all mandated pre-deployment ANAM4TBI assessment data from DoD military personnel through the Office of the Surgeon General, ANAM Program Office to create a research database system which incorporates all these in-person collected, pre-deployment neurocognition assessment data (> 1.5 million ANAM4TBI assessments through Dec 2012). Currently, we are integrating these neurocognitive data with individual military service, demographic, and injury and clinical disease histories.

  At the conclusion of Study 4, we plan to make comparisons between Army Active Duty and National Guard groups and examine the role of deployment-related factors on neurocognitive health and performance.

- Two papers were published during this reporting period; both leveraging the ANAM4 as well as data and resources associated with this project. These papers are as follows and are included in the Appendix:

- A manuscript titled “Adaptation of visual tracking synchronization after one night of sleep deprivation” was published in Experimental Brain Research (online ahead of print) in October 2013. In this paper, predictive visual tracking performance of military volunteers were measured and compared before and after one night of sleep deprivation. The moment-to-moment synchronization of visual tracking during sleep deprivation deteriorated with sensitivity changes greater than 40 %. However, increased anticipatory saccades maintained the overall temporal accuracy with near zero phase error. Results suggest that acute sleep deprivation induces instability in visuomotor prediction, but there is compensatory visuomotor adaptation. Detection of these visual tracking features may aid in the identification of insufficient sleep.

  Full citation: Tong J, Maruta J, **Heaton KJ**, Maule AL, Ghajar J. Adaptation of visual tracking synchronization after one night of sleep deprivation. *Experimental Brain Research*. Published online 11 October 2013. DOI:10.1007/s00221-013-3725-8.

- A manuscript titled 'Dynamic visuomotor synchronization: Quantification of predictive timing' is published in the March 2013 issue of Behavior Research Methods. This methods paper described the indices of a circular visual-tracking paradigm that can be used to assess predictive timing and may be useful for attention assessment. Performance on the tracking paradigm was characterized by variability of gaze positional error relative to the target. Higher gaze-target synchronization indicates better performance, and distributions of the gaze-target synchronization across the study population allowed for the identification of poor performances outside the margin of error determined by test-retest measures.

  Full citation: Maruta J, Heaton KJ, Kryskow EM, Maule AL, Ghajar J. Dynamic visuomotor synchronization: quantification of predictive timing. *Behavioral Research Methods.* 2013, 45(1): 289-300.

REPORTABLE OUTCOMES

Reportable outcomes during the current study period include:

1. Reports, manuscripts, abstracts (included in Appendix)

The following manuscripts were supported in part by this award (W81XWH-08-1-0021):

- Tong J, Maruta J, **Heaton KJ**, Maule AL, Ghajar J. Adaptation of visual tracking synchronization after one night of sleep deprivation. *Experimental Brain Research*. Published online 11 October 2013. DOI:10.1007/s00221-013-3725-8.
- Maruta J, Heaton KJ, Kryskow EM, Maule AL, Ghajar J. Dynamic visuomotor synchronization: quantification of predictive timing. *Behavioral Research Methods.* 2013, 45(1): 289-300.

2. Degrees and research training opportunities

One post-doctoral researcher, two graduate students, and five bachelor's-level research assistants are currently trained to administer the study protocol for this project.

During the current reporting period, a research assistant on this project, applied to and was accepted into a doctoral program in Clinical Psychology and a research coordinator applied to and was accepted into a dual Masters' degree program in Social Work and Public Health.

3. Collaborative funding applications related to work supported by this award

The following funded projects are directly related to the work supported by this award:

- "Eye-Tracking Rapid Attention Computation (EYE-TRAC)" (USARIEM Protocol # H09-07; Site PI: Heaton). This project was funded as a FY08 CDMRP Advanced Technology Award to Dr. Jamshid Ghajar, Brain Trauma Foundation, New York, NY (W81XWH-08-2-0646). This project includes an ANAM4 task battery (ANAM 4 TBI Battery) as part of the protocol, with ANAM 4 data being collected at 4 time points, allowing for computation of test-retest reliability across a 2 week interval and sensitivity of the ANAM4 TBI battery to differentiate performance between a rested and fatigued (24 hour sleep deprivation) state. Data collection is complete; several manuscripts have been published or are currently under review.

- "An Investigation of the Effects of Head Impacts Sustained during Collegiate Boxing Participation on Central and Peripheral Nervous System Function" (USAFA Protocol # FAC2007010H, PI: MAJ Brandon Doan, USAFA), was funded in part by an AMEDD Advanced Medical Technology Initiative (AAMTI) award to Dr. Heaton and includes use of the ANAM4. Data collection is complete; a manuscript has been submitted for peer review.

- "Validation of Select Neurobehavioral Assessments for Concussion/Mild Traumatic Brain Injury (MTBI)" (USARIEM #H09-08), was intramurally funded (MRMC RAD3) to Drs. Proctor and Heaton (co-PIs). This study seeks to validate the ANAM4TBI Battery against a standard neuropsychological screening battery for mild traumatic brain injury. The project is ongoing.

- "Identifying biomarkers that distinguish post-traumatic stress disorder and mild traumatic brain injury using advanced magnetic resonance spectroscopy," was funded via a Department of Defense Congressionally Directed Medical Research Programs Psychological Health/Traumatic Brain Injury (PH/TBI) Research Program award to Dr. Alex Lin, Brigham and Women's Hospital, Boston, MA. Dr. Heaton is a co-Investigator and site PI on this project. This study proposes a multi-parametric approach using major advances on spectroscopic methods and neuroimaging to identify biomarkers that can be used to distinguish between post-traumatic stress disorder, traumatic brain injury, and

their co-occurrence. This will be achieved in part by correlating quantitative MR spectroscopy results with behavioral and neuropsychological metrics (including ANAM4) using newly developed algorithmic approaches that are capable of revealing discriminating metabolic markers in MR spectroscopy measurements. Data collection for this project is ongoing..

4. Related projects and collaborations initiated

"Analyses of ANAM4 TBI predeployment assessment data: USARIEM-OTSG research collaborative" (USARIEM Protocol 11-07-HC) (PI: Dr. Proctor; Co-I: Dr. Heaton)

"Identifying biomarkers that distinguish post-traumatic stress disorder and mild traumatic brain injury using advanced magnetic resonance spectroscopy," (2007-P-002458/9; Brigham and Women's Hospital) Department of Defense U.S. Army Medical Research and Material Command Congressionally Directed Medical Research Programs, 2009 Psychological Health and Traumatic Brain Injury Research Program Award (PI: Dr. Alexander Lin, Brigham and Women's Hospital; Co-I: Dr. Heaton)

Massachusetts Institute of Technology Lincoln Laboratories: collaborations with Dr. Heaton aimed at developing multi-modal assessments for mild TBI/concussion and validation of novel biophysiologic measures of fatigue, brain injury, and stress. This collaboration is ongoing and fruitful.

CONCLUSION

Analyses of data from Studies 1-3 will be completed, and reported, in the coming (final) review period. Our results (reported in conference proceedings included in the 2010 Annual Report for this project) provide evidence supporting the Automated Neuropsychological Assessment Metrics Version 4 (ANAM4) as a reliable and valid measure of cognitive performance under diverse administration scenarios.

Results from Study 4 are pending completion of data collection involving development of a nationally-representative normative dataset of Army National Guard service members' ANAM4 performance outcomes. This dataset is intended to complement existing normative data by focusing on a subset of the general military population that research has shown differs on key demographic elements (e.g., dual career status, average age, marital and family status, education, and so on) relative to other military components (e.g., Active Duty), and as such is expected to facilitate the accuracy of interpretation of individual National Guard service members' performance on ANAM4 tests.

Together, results from all four studies in this project will add to ongoing efforts to develop and validate the ANAM4 as an accurate, reliable and objective measure of military service members' cognitive performance.

APPENDIX

Behav Res (2013) 45:289–300
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Dynamic visuomotor synchronization: Quantification of predictive timing

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Published online: 7 September 2012

Abstract When a moving target is tracked visually, spatial and temporal predictions are used to circumvent the neural delay required for the visuomotor processing. In particular, the internally generated predictions must be synchronized with the external stimulus during continuous tracking. We examined the utility of a circular visual-tracking paradigm for assessment of predictive timing, using normal human subjects. Disruptions of gaze–target synchronization were associated with anticipatory saccades that caused the gaze to be temporarily ahead of the target along the circular trajectory. These anticipatory saccades indicated preserved spatial prediction but suggested impaired predictive timing. We quantified gaze–target synchronization with several indices, whose distributions across subjects were such that instances of extremely poor performance were identifiable outside the margin of error determined by test–retest measures. Because predictive timing is an important element of attention functioning, the visual-tracking paradigm and dynamic synchronization indices described here may be useful for attention assessment.

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Introduction

Visual tracking supports perceptual stability of the object of interest that is in motion. When visually tracking a moving target to maintain its image on the fovea, spatial and temporal predictions are used to circumvent the neural delay required for the visuomotor processing. In particular, the internally generated predictive drive must be synchronized with the external stimulus during continuous tracking, which highlights an important distinction between being able to predict *that* a target will appear at a specific location and being able to predict *when* that event will occur. Accurate predictive timing is the ability to synchronize what is expected with what is observed, which is considered to be a function of attention (Ghajar & Ivry, 2008). Therefore, we investigated whether a visual-tracking paradigm can be used to assess an individual's capacity for predictive timing. A circular visual-tracking paradigm (Umeda & Sakata, 1975; van der Steen, Tamminga, & Collewijn, 1983), with the target traveling at a constant angular velocity with a fixed radius from the center, has a special advantage in that both the spatial and temporal aspects of the target motion are highly predictable. This movement can continue indefinitely within the orbital range of the eye, which makes the stimulus particularly suitable for studying dynamic gaze–target synchronization during predictive visual tracking.

Despite the recent advances in elucidating the neural circuits that convey the visual information to generate pursuit eye movements (see Orban de Xivry & Lefevre, 2009), the precise localization and interrelationships of the neural substrates for the extra-retinal, cognitive components of visual tracking have yet to be determined. However, it is generally assumed that the substrates for these components

are broadly distributed; thus, even a subtle neurocognitive dysfunction could impair visual-tracking behavior. Abnormalities in visual-tracking behaviors have been associated with various psychiatric (Diefendorf & Dodge, 1908; Iacono & Lykken, 1979; Lipton, Levin, & Holzman, 1980) and neurologic (Bronstein & Kennard, 1985; Morrow & Sharpe, 1995; White, Saint-Cyr, Tomlinson, & Sharpe, 1983) disorders, brain lesions (Lekwuwa & Barnes, 1996a, 1996b), and pharmacological effects (Blekher, Miller, Yee, Christian, & Abel, 1997; Rothenberg & Selkoe, 1981).

Using videooculography, eye movement can be monitored easily, precisely, and continuously. Furthermore, oculomotor paradigms are resilient to inconsistent or poor subject effort (Heitger et al., 2009). However, to evaluate specific visual-tracking abnormalities in a quantitative manner, characterization of normal behavior using a well-defined testing paradigm is necessary. Visual-tracking performance should then be objectively quantified using standardized parameters such as smooth pursuit velocity gain, phase error, and root-mean-square (RMS) error. Impairments in visuomotor synchronization may also be assessed by variability of gaze positional error relative to the target (Maruta, Lee, Jacobs, & Ghajar, 2010; Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010).

Our interest in developing a rapid assessment of attention in concussion patients has led to the use of a circular visual-tracking paradigm (Maruta, Lee, et al., 2010; Maruta, Suh, et al., 2010). The diagnosis of concussion, or mild traumatic brain injury (TBI), is made difficult by symptoms that are often subtle and transient. Although impaired attention is a hallmark of TBI (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Stuss et al., 1989), the impairment can go undetected by traditional neurocognitive measures that rely on verbal or motor responses to discrete stimuli and are sensitive to subject motivation and effort.

The use of a visual-tracking paradigm for attention assessment is based on the hypothesis that attention impairments in concussion patients are a consequence of reduced efficacy of predictive timing (Ghajar & Ivry, 2008). Our approach is supported by the evidence that eye movement and attention processes are implemented by closely overlapping areas of the brain (Corbetta et al., 1998) and that attention is required during visual tracking (Baumann & Greenlee, 2009; Chen, Holzman, & Nakayama, 2002). Our previous study of circular visual tracking in concussed patients suggested that impaired predictive timing, rather than disengagement from prediction, can result in poor tracking (Maruta, Suh, et al., 2010). This study also supported that impaired visual-tracking performance was related to injury of attention-related anatomical locations and diminished neurocognitive performance.

The primary goal of this study is to describe the indices and normal variations of dynamic visuomotor synchronization during circular visual tracking in healthy, young adult subjects, from which the criteria for abnormal performance can be derived. In addition, because the clinical utility of a test is ultimately limited by the reliability of its measurements, we aim to establish the test–retest reliability of the visual-tracking measures.

Method

The present study, utilizing a prospective, repeated measurement design, was conducted at the United States Army Research Institute of Environmental Medicine (USARIEM) located at the Natick Soldier Center, Natick, MA, as part of a clinical research award to Brain Trauma Foundation, New York, NY. The protocol was reviewed and approved by the USARIEM Human Use Review Committee and the USARIEM Office of Research Quality and Compliance. Written informed consent was obtained from all subjects prior to data collection.

Subjects

The subjects in this study were military volunteers recruited for a larger ongoing study of the effects of sleep-deprivation-induced fatigue on neurocognitive function. The visual-tracking data presented in this report were collected during two test sessions separated across a 14-day interval while subjects were rested. Both sessions took place in the morning (0630–0930) in order to control for the circadian effects and to coincide with subjects' typical morning schedules.

Potential subjects were recruited via scheduled, in-person briefings. Eligibility criteria included having no prior history of head injury with loss of consciousness, no substance abuse problems/treatment, no known neurological disorders, no major psychiatric disorders (including attention deficit hyperactivity disorder [ADHD]), and no gross visual (no worse than 20/30 corrected or uncorrected) or hearing problems. Participation was limited to men and women 18–50 years of age who had completed at least 12 years of education and were able to abstain from caffeine use for at least 26 h. Prospective subjects underwent a structured screening interview conducted by a member of the research staff. This screening interview consisted of the Conners Adult ADHD Rating Scale–Self-Report: Short Version (CAARS–S:S; Pearson, San Antonio, TX), the Post Traumatic Stress Disorder (PTSD) Checklist–Civilian Version (PCL–C; National Center for PTSD, U.S. Department of Veterans Affairs), the Center for Epidemiologic Studies Depression Scale (CES–D; Radloff, 1977), and the Brain Injury Screening Questionnaire (BISQ; Gordon, Haddad, Brown, Hibbard, & Sliwinski, 2000). Exclusion criteria consisted of a *t*-score of >70 on the CAARS–S:S or a positive result for brain injury on the BISQ. Family history of psychiatric disorders was not assessed.

A total of 50 subjects were enrolled in this study. Three subjects withdrew from the study after enrollment because of scheduling conflicts. Demographic information for the remaining 47 subjects is presented in Table 1.

Eye movement recording

The visual-tracking protocol was implemented on an apparatus that integrated stimulus presentation and eye tracking (EyeLink CL, SR Research, Ontario, Canada). Prior to testing, an eye chart was used to verify that the subject had normal or corrected-to-normal vision. The subject was seated in a normally lit room with the head stabilized using a head- and chinrest during testing. The visual stimulus was presented using a 120-Hz frame rate LCD monitor (Samsung SyncMaster 2233RZ; see Wang & Nikolić, 2011) placed 47.5 cm from the subject's eyes. The monitor area subtended 53° (horizontal) by 35° (vertical) in visual angles with a resolution of 0.033°/pixel. Movements of both eyes were recorded under binocular viewing conditions with a sampling frequency of 500 Hz with a single desktop camera while the subject's face was illuminated with an array of infrared LEDs.

The test stimulus consisted of a red circular target, 0.5° diameter in visual angle with a 0.2° black dot in the center. The target moved in a circular clockwise trajectory of 10° radius at 0.4 Hz against a black background, with the target speed corresponding to 25°/s. The stimulus fell in the frequency range within which progressive degradation of performance occurs in normal subjects (Barnes, 2008).

Table 1 Subject demographics

	Mean	*SD*
Age (years)	21.2	3.5
Education (years)	12.5	1.2
Time active in army (months)	9.1	3.4
CAARS–S:S Index	40.0	7.0
PCL–C total score	21.3	5.9
CES–D total score	5.9	4.7
	N	Percentage
Gender		
Male	35	74.5
Female	12	25.5
Ethnicity		
White (Caucasian)	24	51.1
Black (African-American)	12	25.5
Hispanic or Latino	10	21.3
Other	1	2.1
Rank		
Private	1	2.1
Private II	32	68.1
Private First Class	12	25.5
Specialist	2	4.3

The testing sequence lasted approximately 5 min and consisted of a practice run, calibration, and two consecutive recorded test runs. Standardized instructions for completion of the test were presented both visually on the computer monitor and aurally via the attached audio speakers. Additional audio cues (such as "beeps" and "clicks") were provided to facilitate the testing process. No audio cue was provided during the tracking task, however. Although largely automated, the testing protocol required intervention by the experimenter to enter relevant information, adjust the camera, and initiate the calibration procedure.

Calibration of the eye position was conducted by having the subject fixate on a target presented at eight locations on the circular path of the test stimulus and one additional fixation point at the center of the circular path. The fixation target was presented at these nine locations in a randomized order. When an error was suspected or detected at any location, the target was presented there again. The calibration was validated by presenting the fixation target at the nine locations in a similar fashion.

The practice run included two cycles of circular target movement identical to the subsequent test runs except in the number of cycles. Each of the two test runs consisted of six cycles of circular movement corresponding to 15 s in duration per test run. With both practice and test runs, the target was presented at the central location to serve as a visual fixation point prior to and following the circular movement of the target. The instruction for the tracking task was "follow the movement of the target as closely as possible." Target analysis, which is known to improve visual-tracking performance (Holzman, Levy, & Proctor, 1976; Shagass, Roemer, & Amadeo, 1976; Van Gelder, Lebedev, Liu, & Tsui, 1995), was not part of the testing procedure.

Eye movement analysis

Eye movement data were analyzed using a custom MATLAB program (The MathWorks, Natick, MA, USA). As described below, a single set of performance indices was obtained for each testing session that included two brief repeated test runs, although between-trial variations were also considered. The eye and target positions were expressed in visual angle. Blinks and other events during which the pupil was occluded were identified by the computer program and excluded from further analyses. To compensate for any potential artifact caused by unwanted head drifts relative to the camera during eye movement recording, the differences between the recorded gaze positions and the central fixation point presented before and after the circular target movement were calculated. The offset in the horizontal and vertical eye positions caused by a head drift was

estimated with a linear interpolation between the pre- and post-run fixation differences and digitally subtracted from the data. In practice, however, the drift measured during each 15-s trial had an average of 0.50° in total visual angle with a standard deviation (*SD*) of 0.49°; thus, a correction would have been unnecessary in most cases.

To visualize gaze positional errors relative to the target motion, the target position was expressed in polar coordinates, and both the target and eye positions were rotated so that the target was at the 12 o'clock position (Fig. 1b). In this reference frame, the distance between the origin and the gaze represented the instantaneous radius of the gaze trajectory, and the angle formed by the vertical axis and the gaze vector represented the phase difference between the target and the gaze—that is, phase error. Positive phase error was defined as the gaze leading the target.

We quantified intraindividual variability in visual-tracking behavior using the *SD* of gaze positional errors relative to the target (Maruta, Suh, et al., 2010). The variability in the radial direction was measured with the *SD* of gaze errors perpendicular to the target trajectory, whereas the variability in the tangential direction was measured with the *SD* of gaze errors along the target trajectory. To facilitate comparison, the error variability measures were expressed in visual angle for both the radial and tangential directions. The radial error corresponds to the deviation in the radius of the gaze trajectory from the circular trajectory of the target, and the tangential error is proportional to the phase error.

Horizontal and vertical eye position data were two-point differentiated to obtain eye velocity, which was smoothed with a ten-point moving average filter. The signal was further differentiated to obtain eye acceleration, which was smoothed with a five-point moving average filter. Saccades were detected with velocity and acceleration thresholds of 100°/s and 1,500°/s^2, respectively, and the saccade segments in the velocity data, which were expressed as sharp spikes, were replaced with straight lines connecting the ends of the remaining segments. The saccade detection thresholds took into consideration that saccades were generated during pursuit rather than fixation. Eye position and velocity traces were visually displayed by the analysis program, and the accuracy of saccade detection was verified.

To measure the level of accuracy in matching the eye velocity to the target velocity, smooth pursuit velocity gain was computed. The amplitudes of horizontal and vertical velocity modulations were obtained by fitting the desaccaded velocity traces with sine curves of the frequency of the circular movement of the target, using fast Fourier transformation. The fitted traces were overlaid on the eye velocity traces in the software interface and visually matched with the smooth pursuit velocity modulations. Horizontal and vertical gains were the ratios between the amplitudes of the respective components of eye and target velocities.

To obtain a metric equivalent to the combination of horizontal and vertical smooth pursuit gain, phase error data were two-point differentiated and smoothed with a ten-point moving average filter. Instantaneous angular velocity gain was expressed as unity plus the ratio of phase error velocity to the constant angular velocity of the target. Average smooth pursuit angular velocity gain was then calculated by excluding saccade segments.

To measure the level of positional precision of visual-tracking performance in horizontal and vertical directions, RMS positional deviations of the gaze from the target were calculated for the respective directions. The *SD*s of radial and tangential errors, mean phase error, angular smooth pursuit gain, and RMS errors were computed from the combination of the two test trials included in each test sequence. The horizontal and vertical gain values were computed for each trial and then averaged. The data segments from the first cycle of each test run were discounted from the analysis so that the transient response to the initial target movement was excluded.

Eye movement was recorded binocularly. A pilot analysis of the day 1 data with Pearson's *r* calculated for the five visual-tracking parameters showed a high correlation between the left and the right eyes (range .90–.99). However, only monocular data were pooled for further analyses. The use of monocular data was based on the following rationale: Generally, small radial error variability provides an indication of spatial accuracy in the recorded data, since it combines the effects of a high level of performance by the subject and accurate eye position calibration. The eye-tracking equipment utilized in this study employed a single camera to record both eyes; thus, the spatial accuracy of eye position calibration in our data may have been compromised by the placement of the camera relative to each eye. To focus on the records that likely better represented the subject's performance, the data from the eye with the smaller *SD* of radial errors were used for further analyses. This routine is justified because ocular dominance may have little relevance to the level of visual-tracking performance (Bahill & McDonald, 1983).

Statistical analysis

Characterization of visual-tracking performance was aided by the following statistical procedures. Pearson's correlation coefficient *r* was computed to determine the level of linear dependence between test–retest measurements and between parameters. A paired *t*-test was used to test against the null hypothesis that no systematic difference existed between measurements (46 degrees of freedom [*df*]). The alpha level was set at $p = .05$. The use of the *t*-test for the test–retest analysis is justified because a single set of performance indices was associated with each testing session. That no significant between-trial effect existed was confirmed using a two-way repeated measure analysis of variance (ANOVA).

The intraclass correlation coefficient (ICC) with one-way random effect model was computed to determine the level of test–retest agreement (Bartko, 1966). ICC ranged from 0 to 1, with the latter value indicating a perfect match. Since the computation of ICC assumes normality of the data and is biased by the skewness of the data, the raw data were transformed with a Box–Cox transformation. The parameter of the transformation was chosen so that the absolute value of the skewness of the distribution of the transformed data was minimized. All measurements except those for mean phase error have positive values. The values for the mean phase error parameter was first offset by a constant value obtained by doubling the minimum (negative) value before the application of the Box–Cox transformation.

In addition to assessing the relative reliability with ICC, the absolute reliability of the visual-tracking test was assessed by analyzing the distribution of test–retest differences defined as the value for the second measurement minus that for the first. When the differences (ΔX) follow a normal distribution, approximately 95 % of ΔX should lie within the mean ± 1.96 *SD*, which constitutes the 95 % confidence interval of repeatability (Bland & Altman, 1986, 1999). This analysis does not assume any specific shape of the distribution of the measurements *X*.

The Bland–Altman method was also used to assess the absolute agreement between smooth pursuit angular velocity gain and combinations of horizontal and vertical smooth pursuit velocity gains. The 95 % confidence interval of the difference was calculated from within-individual test–retest means of these gain parameters.

Results

Performance characteristics

Despite the highly predictable nature of the target movement, visual tracking was generally imperfect. A typical performance is illustrated in Fig. 1. The map of the gaze mimicked the circular path of the target, but variability of the gaze positional error described by the radius was evident (Fig. 1a). When the gaze trajectory was redrawn in a polar coordinate reference frame defined relative to the target (Fig. 1b), variability in gaze position error, tangential (parallel) to the target trajectory, also became evident. The spread in the tangential direction accounted for temporal variability, with the gaze falling ahead (clockwise shift) or behind (counterclockwise shift) the target moving at constant velocity (but fixed at the 12 o'clock position in the figure illustration).

In all subjects, eye position modulation during visual tracking involved a mixture of saccadic and smooth pursuit components (Fig. 1c, d). Accordingly, the eye velocity traces had saccadic spikes superimposed on a smooth sinusoidal modulation (Fig. 1e, f). Most of the large saccadic spikes occurred in the direction of and near the peaks and troughs of the smooth modulation, indicating that these saccades were in the forward direction of the target motion. Consistent with this observation, the phase error trace had a sawtooth waveform with repetitive positive-driving fast components (Fig. 1g). The end points of forward saccades rarely landed in phase with the target and appear to be randomly distributed. The end points of saccades in the radial direction were also inconsistent (not shown); thus, saccades generally did not reduce gaze positional errors to serve corrective functions. The origination points of saccades were similarly inconsistent, apparently suggesting a lack of any threshold for triggering that is associated with positional errors.

The distributions of the visual-tracking parameters were skewed so that most subjects performed with better-than-average accuracy and the range of the distribution was extended by infrequent large deviations (Table 2). Smooth pursuit angular velocity gain was comparable to the combination of horizontal and vertical smooth pursuit gain. The 95 % confidence intervals of the differences from the arithmetic or quadratic means of horizontal and vertical smooth pursuit velocity gains were only 0.006 ± 0.046 and 0.004 ± 0.018, respectively.

To compare the accuracy of horizontal and vertical tracking, the test–retest means of the respective components for gain and RMS errors were plotted for each individual (Fig. 2). The dotted diagonal lines in Fig. 2 represent equivalence between horizontal and vertical components. For the most part, the vertical gain values fell below the diagonal lines (left panel) and the vertical RMS errors above the diagonal lines (right panel), both showing better accuracy in the horizontal direction. The mean horizontal gain was significantly higher than the mean vertical gain (paired *t*-test, *t*-value > 9.55, $df = 46$, $p < 10^{-11}$), and the mean horizontal RMS error was significantly lower than the mean vertical RMS error (paired *t*-test, *t*-value < −6.55, $df = 46$, $p < 10^{-7}$).

Although horizontal tracking tended to be more accurate, there were associations both between horizontal and vertical gains ($r = .85$) and between horizontal and vertical RMS errors ($r = .98$) (Fig. 2). Thus, a poor performer in the horizontal dimension was also a poor performer in the vertical dimension in either the positional or the velocity domain, suggesting interdependence between horizontal and vertical eye movements.

While highly synchronized visual tracking was accompanied by saccades that were usually smaller than 1° of visual angle in amplitude, relative to the moving target, some subjects displayed tracking that featured large forward saccades that exceeded 10° (Fig. 3). When drawn relative to the target position, the trajectories of large saccades and smooth components often took the shape of the chord and the arc of a circular sector, respectively. Although the velocity of the target provides an important drive for the ensuing visual

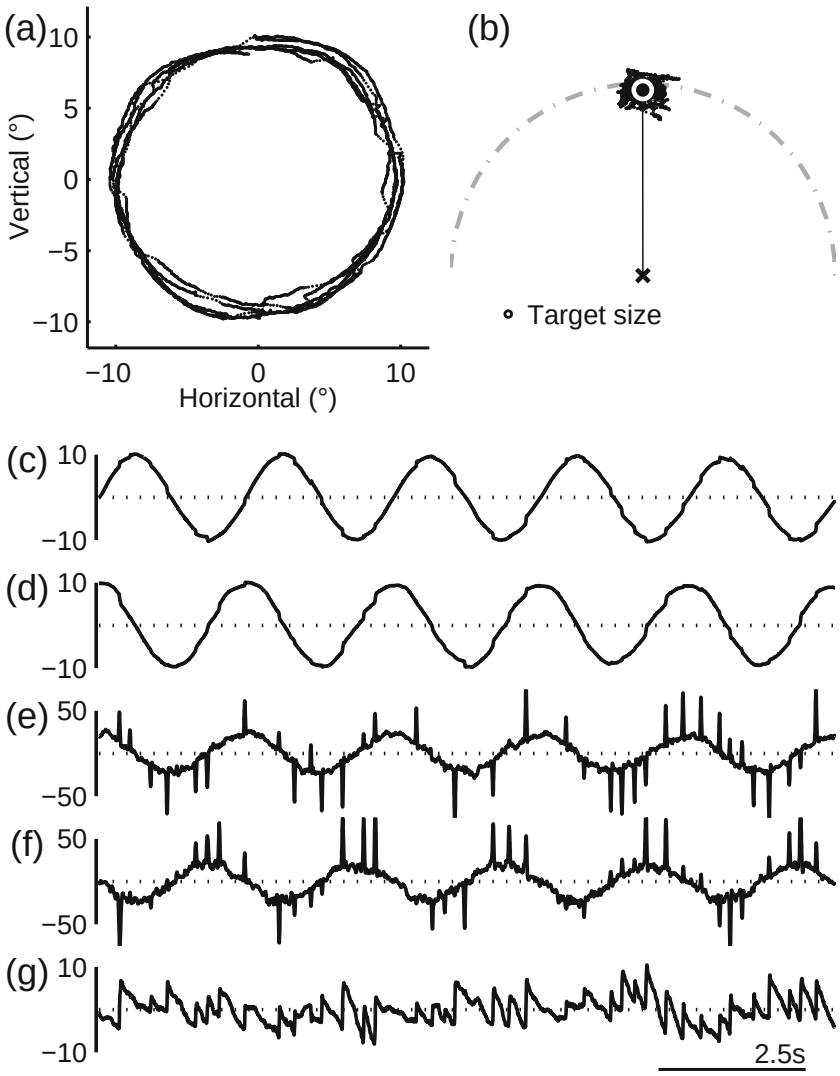

Fig. 1 Typical visual-tracking performance during which a target moved in a circular trajectory of 10° radius at 0.4 Hz (Subject 046). **a** Two-dimensional trajectory of the gaze. **b** Scattergram of gaze positions relative to the target fixed at the 12 o'clock position. The center of the *white circle* indicates the average gaze position. The *dot-dashed curve* indicates the circular path. A proportionally sized target is drawn at the bottom. **c** Horizontal eye position (°). **d** Vertical eye position (°). **e** Horizontal eye velocity (°/s). **f** Vertical eye velocity (°/s). **g** Phase error relative to the target (°). A positive phase indicates lead

Table 2 Test–retest statistics

	SD radial errors	*SD* tan-gential errors	Mean phase	H gain	V gain	Angular velocity gain	RMS_H	RMS_V
Min	0.30°	0.36°	−4.48°	0.26	0.20	0.18	0.28°	0.35°
Max	2.05°	4.92°	17.78°	1.00	1.04	0.98	4.23°	5.62°
Mean Δ	0.03°	0.01°	−0.25°	0.00	0.00	−0.01	0.00°	−0.09°
r	.77	.87	.93	.89	.81	.88	.87	.88
ICC	.68	.63	.64	.75	.71	.76	.67	.62
95 % CI	±0.46°	±0.76°	±2.56°	±0.11	±0.16	±0.12	±0.60°	±0.74°
Mean	0.62°	0.89°	−0.40°	0.88	0.79	0.85	0.66°	0.93°
Median	0.52°	0.66°	−1.15°	0.92	0.82	0.88	0.53°	0.75°
5th worst	0.98°	1.35°	0.35°	0.80	0.65	0.74	1.08°	1.27°
2nd worst	1.68°	3.89°	12.40°	0.69	0.53	0.63	2.62°	2.01°

Top section: Minima and maxima, mean test–retest differences (Δ), and test–retest correlations (Pearson's *r*) of circular visual-tracking parameters, ICC of the respective data set after normalization, and widths of the 95 % confidence intervals of repeatability. Bottom section: Summary statistics of the distributions' within-individual averages

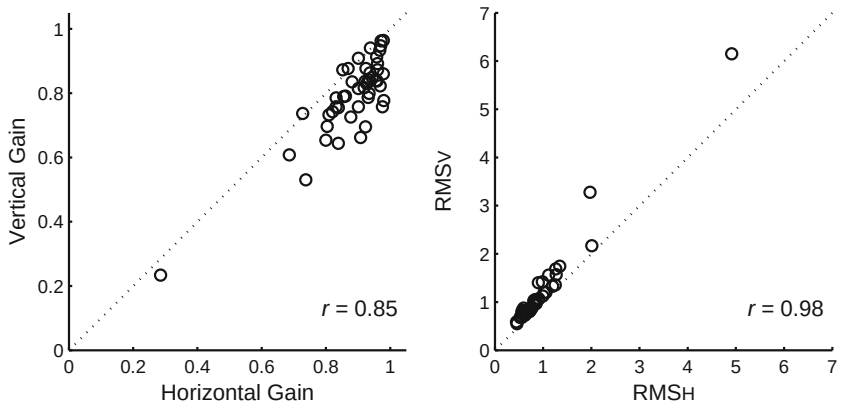

Fig. 2 Relationship between horizontal and vertical tracking. *Left*: Gains. *Right*: RMS errors

tracking, the direction of these large saccades clearly deviated from that of the instantaneous velocity of the target (Fig. 3b–d), which extended along the tangent of the target trajectory (horizontally in Fig. 3). Instead, large saccades anticipated the future path of the target. After landing ahead of the target, the gaze continued to move in the forward direction of the target movement, but at a slower velocity than the target, which slowly brought the gaze position closer to the target.

These large saccades not only caused large gaze positional errors in both radial and tangential directions, but also contributed to an increase in gaze positional error variability in these directions. However, as was noted above, these saccades were anticipatory, and the positional variability was larger in the tangential direction, which is the dimension that accounts for temporal variability. In addition to variability, the presence of large saccades had the effect of driving the mean phase error positive (Fig. 3c, d), because forward saccades in general were repetitive and occurred before there was a substantial lag in the gaze position relative to the target (Fig. 1g).

The presence of large saccades was also linked to low smooth pursuit velocity gain because of the reduced contribution by the smooth pursuit component in the overall tracking. Even so, the simple gain measures could not capture the dynamic interaction of saccade and smooth pursuit components of visual tracking. Similarly, the presence of large saccades was linked to large RMS errors, but the relationship between RMS errors and the tracking dynamics is indirect because RMS errors are sensitive to a phase offset; that is, even a perfect synchrony with a constant phase would yield a large error value. Therefore, although smooth pursuit gains and RMS positional errors are good measures for characterizing the overall accuracy of matching the gaze velocity or position to the target, the *SD* of positional errors in the tangential direction and mean phase error are better suited for characterizing the temporal dynamics of visuomotor synchronization.

Measurement reliability

Any measurement is only an estimate of the true value that represents the subject. The accuracy of such estimates depends on the reliability of the measurement method, which

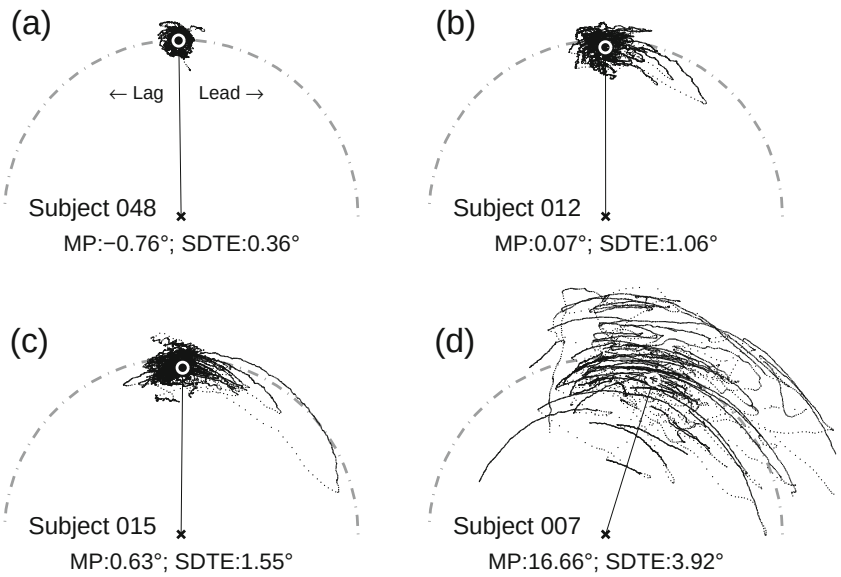

Fig. 3 Different grades of visual-tracking performance. **a**–**d** Increases in positional error variability. The scattergrams follow the same convention as that in Fig. 1b. Each dot corresponds to a sample taken at 500 Hz; consequently, saccade trajectories are represented by series of discrete dots. MP, mean phase error (expressed in phase angle); SDTE, *SD* of tangential errors (expressed in visual angle)

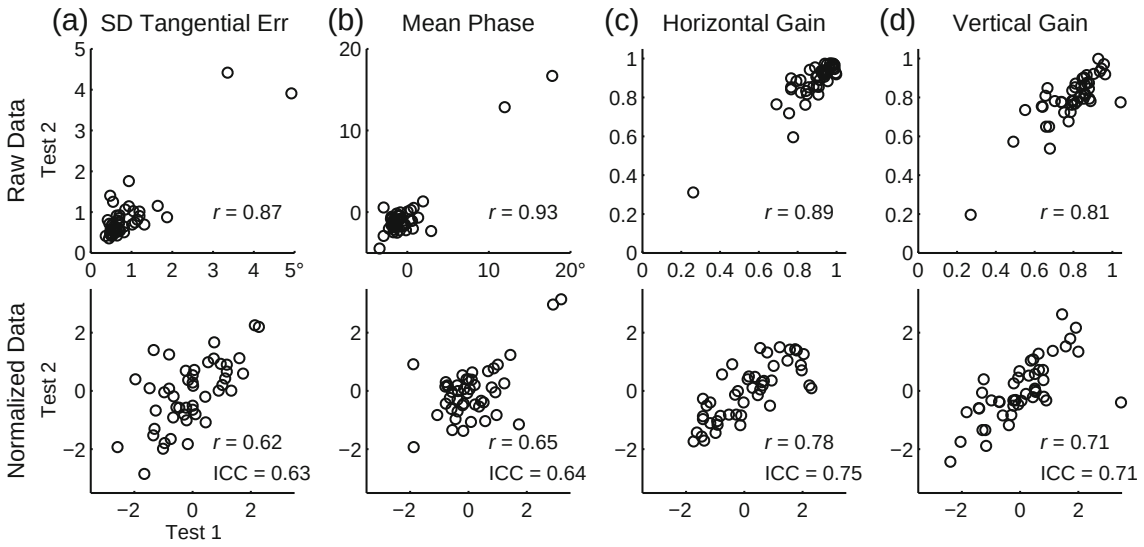

Fig. 4 Test–retest correlograms of raw and normalized data. **a** *SD* of tangential errors. **b** Mean phase error. **c**, **d** Horizontal and vertical gains of smooth pursuit velocity. *Top row*: Raw data. *Bottom row*: Data normalized with Box–Cox transformations and rescaled as *Z*-scores

can be indicated by how closely two measurements taken from each subject agree. Figure 4 shows example test–retest correlations of raw and normalized data. Pertinent statistics for all the visual-tracking parameters we examined are listed in Table 2. The ICC ranged from .62 to .76, indicating moderate to strong test–retest agreement.

To further characterize the reliability of the measurements, within-individual test–retest differences were analyzed. Paired *t*-test did not detect any significant difference between the measurements taken 2 weeks apart (absolute t-value < 1.65, df = 46), and the mean differences were essentially zero (Table 2, mean Δ). A two-way repeated measure ANOVA showed no statistically significant effect of testing session, trial, or interaction in any of the visual-tracking performance indices [test session, $F(1, 46) < 2.94$; trial, $F(1, 46) < 0.37$; interaction, $F(1, 46) < 2.13$]. Therefore, only the variability of test–retest difference was determined to be essential to the analyses of agreement between the measurements from the two test sessions, which can be expressed as the widths of 95 % confidence intervals of repeatability (Table 2). The 95 % confidence interval indicates the range beyond which, given the value of a single measurement, the value of a second measurement from the same subject is unlikely to fall.

Associated with each measurement is a 95 % confidence interval defined about the measured value. The accuracy of the estimate of how a measurement compares in the population in terms of percentile can be evaluated by sliding the 95 % confidence interval along the cumulative distribution plot (Fig. 5). Since percentile values changed rapidly relative to the change in the measured values among high- and average-level performances, the ranges covered by the 95 % confidence intervals in these regions encompassed a large portion of the subject population. Thus, the ability of the visual-tracking test to differentiate high- and average-level performances was low. On the other hand, the individuals represented at the long tail of the distribution stood apart from the majority. The values for the worst two performers were outside the 95 % confidence interval around the median value in all of the visual-tracking parameters (Table 2).

Discussion

In this study, we described a method and indices for characterizing predictive timing using a circular visuomotor synchronization paradigm. The use of circular target motion provided spatial and temporal information of visuomotor prediction. The continuous circular paradigm also precluded the limits on the timing and amplitude of anticipatory saccades imposed by end points that exist in a one-dimensional tracking paradigm (Van Gelder et al., 1995). In addition to some of the standard measures, such as smooth pursuit velocity gain, phase error, and RMS error, we measured the variability of gaze positional error relative to the target. Quantifying performance variability is essential since a dysfunction in predictive timing should increase performance variability. Positional error variability is a useful index in concussion studies since TBI is known to increase intra-individual performance variability on visuomotor tasks (Robertson et al., 1997; Stuss et al., 1989).

Although our subject cohort was limited to healthy enlisted soldiers with similarities in age, training, and physical conditioning, the spatial and temporal accuracy of prediction varied among the subjects. However, the intraindividual test–retest measurements that were taken 2 weeks apart were strongly correlated. Such stability over time suggests that

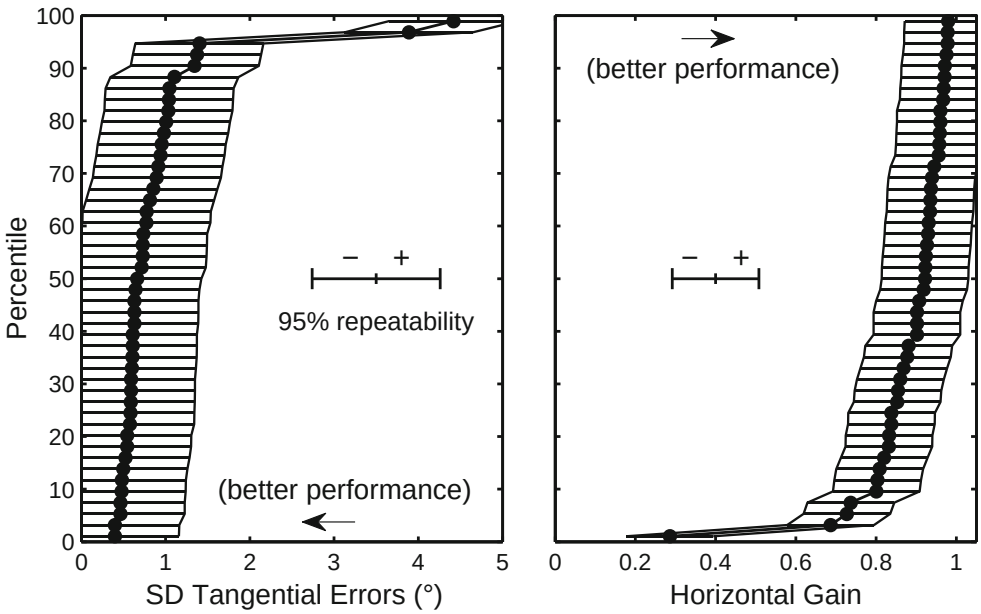

Fig. 5 Cumulative distributions of visual-tracking parameters. *Left*: *SD* of tangential errors. *Right*: Horizontal gain. Each *filled circle* represents a subject. The *scale bars* indicate the 95 % confidence interval of repeatability

interindividual variations in visual-tracking performance are based on neurological differences. These variations in visual-tracking performance should provide insight into the spectrum of cognitive functioning between individuals. Furthermore, a change in visual-tracking performance within an individual may indicate a change in the person's neurological state.

Accuracy of spatial prediction

Visual tracking was more accurate in the horizontal than in the vertical direction. This finding is consistent with previous reports (Collewijn & Tamminga, 1984; Rottach et al., 1996) and points to separate mechanisms of control for horizontal and vertical tracking. Because little noise is introduced in the final motor pathways (Lisberger, 2010), the difference between horizontal and vertical accuracies cannot be wholly explained by a difference in the brainstem motor nuclei. The eye muscle geometry, however, may place a larger computational load for vertical control to conform to Listing's law during motor planning (Angelaki & Dickman, 2003; Boeder, 1962; Simpson & Graf, 1981); therefore, it is possible that this larger computational load at the premotor stage contributes to decreased accuracy. The difference between horizontal and vertical tracking may also be generated at the level of visual processing, since there is a large contribution of sensory errors to the noise in the visuomotor response (Osborne, Lisberger, & Bialek, 2005).

Although there were differences in horizontal and vertical tracking, performance levels in the horizontal and vertical directions were parallel within individuals. Similar results have been demonstrated in clinical populations, including people diagnosed with schizophrenia and with bipolar disorder (Lipton et al., 1980). Research on infants also shows interdependence between the development of horizontal and vertical visual tracking mechanisms (Grönqvist, Gredebäck, & Hofsten, 2006). Taken together, these findings suggest a hierarchy of visuomotor processing and the existence of a high-level mechanism of control for horizontal and vertical visual tracking whereby computations are carried out in the two-dimensional visual space. This argument is consistent with the notion that visual tracking requires complex cognitive processes that are mediated by the cerebral cortex (Barnes, 2008; Chen et al., 2002; Kowler, 2011; Krauzlis, 2005; Lipton et al., 1980).

Accuracy of temporal prediction: Predictive timing

Evidence for the functional linking of vertical and horizontal tracking lends validity to our use of visual-tracking parameters based on polar coordinates. These parameters are uniquely associated with circular tracking, as opposed to linear or more complex two-dimensional tracking. With a precise method of eye position recording, large variability in the instantaneous radius of gaze trajectory (radial error variability) must indicate instability in the subject's spatial control, while large variability in the instantaneous angular phase (tangential error variability) must indicate a compound effect of instabilities in spatial and temporal control. Mean phase error, on the other hand, is an indicator of overall temporal accuracy. In a highly predictable circular tracking task, tangential error variability and mean phase error point to the individual's ability to sustain the state of synchronization between the external stimulus and the internally generated predictive drive.

We found that increases in phase lead, not lag, were associated with decreases in tracking accuracy assessed by gaze error variability, gain, and RMS errors. During tracking, the phase error was modulated with a sawtooth pattern, interposed by forward saccades. Poor tracking was characterized not by the mere presence of forward saccades but by the large and variable amplitudes of these saccades. Large forward saccades were anticipatory rather than corrective, landing as much as >10° of visual angle ahead of the target in some subjects. While catch-up saccades—that is, corrective forward saccades—compensate for phase lag, anticipatory saccades produce phase lead (Van Gelder et al., 1995). Since forward saccades repeatedly occurred before the gaze lagged the target sufficiently to offset the lead, the presence of large anticipatory saccades was associated with a large mean phase lead.

In our healthy subject cohort, we found no evidence for consistent positional errors that could serve as a threshold for initiating forward saccades during circular tracking. The saccades could not have been generated in reaction to the target image falling out of the foveal range, because the degrees of phase lag were generally smaller than those corresponding to the known range of latency for reactive saccades (Barnes, 2008; Rashbass, 1961; Westheimer, 1954). Thus, forward saccades must be triggered by an internal mechanism. It is possible that instability is induced when a high smooth pursuit eye velocity is generated, which can be ameliorated by generating large forward saccades, leading to slower velocities and greater stability.

Another possible explanation lies in the mechanism of attention. Attention is or can readily be allocated ahead of a moving target during predictive visual tracking (Khan, Lefèvre, Heinen, & Blohm, 2010; Lovejoy, Fowler, & Krauzlis, 2009; van Donkelaar & Drew, 2002). Such attention allocation is usually covert in that the gaze is maintained on the target; that is, the urge to shift the gaze to the center of attention away from the target is suppressed. It is possible that anticipatory saccades are the results of a failure in the top-down suppression mechanism, analogous to errors in antisaccade paradigms wherein suppression of reflexive automatic prosaccades is required (Munoz & Everling, 2004). In congruence with this hypothesis, the role of the right prefrontal cortex has been implicated in predictive visual tracking (Lekwuwa & Barnes, 1996a; Maruta, Suh, et al., 2010), antisaccade performances (Ettinger et al. 2008; Hwang, Velanova, & Luna, 2010), and attentional control (Corbetta & Shulman, 2002). Thus, a visual-tracking performance marked by excessive anticipatory saccades would suggest a neurologic dysfunction distinct from those marked by an increase in phase lag (Bronstein & Kennard, 1985; Heide, Kurzidim, & Kömpf, 1996; Keating, 1991; Lekwuwa & Barnes, 1996a, 1996b). Visual tracking of patients with chronic concussive syndrome (PCS) typically includes anticipatory saccades and phase lead (Maruta, Suh, et al., 2010) and, consistent with the hallmark symptom of PCS, attention impairments.

Measurement reliability

In the present study, changes in visual-tracking parameter measurements were observed between tests in individual subjects. Both errors associated with the measurement equipment and the inherent variability in motor behavior contribute to changes in measurements; therefore, the interpretation of these measurements needs to take measurement reliability into consideration. It has been argued that Pearson's product–moment correlation coefficient r is an inappropriate measure of reliability because r is an index for association, not agreement, between two variables (Bartko, 1991; Bland & Altman, 1986). ICC, a commonly used index of relative reliability, also fails to describe the precision with which a measurement can be clinically interpreted—that is, absolute reliability. We addressed absolute reliability with the use of the 95 % confidence interval of repeatability associated with each of the visual-tracking parameters.

The smaller the 95 % confidence interval of repeatability, the more precise the measurement is. However, the precision required to distinguish a measurement as different from other measurements depends on the value of the measurement in relation to the shape of the parameter distribution. Because of the skew characteristics of the visual-tracking parameter distributions, the relative precision was low for the range applicable to most subjects but high for values associated with a few extremely poor performers. Consequently, instances of extremely poor performances were salient and were identifiable outside the margin of error within the normal subject group. Given that our primary goal of using visual-tracking assessment is to delineate the normal population and, as a result, identify exceptions, the method and indices described in this study have potential utility in quantifying and monitoring attention function involved in dynamic visuomotor synchronization. This approach will gain further strength as normative standards become better defined with consideration of factors such as age and gender.

Conclusion

We quantified the performance of maintenance-period predictive circular visual tracking using several measures. Successful visual tracking requires dynamic cognitive synchronization of the internally generated prediction with the external stimulus, yet we found varying degrees of visuomotor synchronization among normal subjects. Disruptions of gaze–target synchronization were associated with anticipatory saccades that

suggested impaired predictive timing. Within the ranges of variations in the synchronization indices, there was a clear difference between good and poor performers. The interindividual performance variability likely reflects varying levels of attentional control among individuals. Thus, quantification of dynamic visuomotor synchronization in an individual may provide a sensitive and reliable attention metric. The quantification of circular visual-tracking performance provided here establishes the essential testing parameters for assessing normal and impaired attention.

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References

Angelaki, D. E., & Dickman, J. D. (2003). Premotor neurons encode torsional eye velocity during smooth-pursuit eye movements. *Journal of Neuroscience, 23,* 2971–9.

Bahill, A. T., & McDonald, J. D. (1983). Smooth pursuit eye movements in response to predictable target motions. *Vision Research, 23,* 1573–83.

Barnes, G. R. (2008). Cognitive processes involved in smooth pursuit eye movements. *Brain and Cognition, 68,* 309–26.

Bartko, J. J. (1966). The intraclass correlation coefficient as a measure of reliability. *Psychological Reports, 19,* 3–11.

Bartko, J. J. (1991). Measurement and reliability: Statistical thinking considerations. *Schizophrenia Bulletin, 17,* 483–489.

Baumann, O., & Greenlee, M. W. (2009). Effects of attention to auditory motion on cortical activations during smooth pursuit eye tracking. *PLoS One, 4,* e7110. doi:10.1371/journal.pone.0007110

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet, 1*(8476), 307–10.

Bland, J. M., & Altman, D. G. (1999). Measuring agreement in method comparison studies. *Statistical Methods in Medical Research, 8,* 135–60.

Blekher, T., Miller, K., Yee, R. D., Christian, J. C., & Abel, L. A. (1997). Smooth pursuit in twins before and after alcohol ingestion. *Investigative Ophthalmology & Visual Science, 38,* 1768–73.

Boeder, P. (1962). Co-operative action of extra-ocular muscles. *British Journal of Ophthalmology, 46,* 397–403.

Bronstein, A. M., & Kennard, C. (1985). Predictive ocular motor control in Parkinson's disease. *Brain, 108,* 925–40.

Chen, Y., Holzman, P. S., & Nakayama, K. (2002). Visual and cognitive control of attention in smooth pursuit. *Progress in Brain Research, 140,* 255–65.

Collewijn, H., & Tamminga, E. P. (1984). Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. *The Journal of Physiology, 351,* 217–50.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Review Neuroscience, 3,* 201–15.

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., et al. (1998). A common network of functional areas for attention and eye movements. *Neuron, 21,* 761–73.

Diefendorf, A. R., & Dodge, R. (1908). An experimental study of the ocular reactions of the insane from photographic records. *Brain, 31,* 451–492.

Ettinger, U., Ffytche, D. H., Kumari, V., Kathmann, N., Reuter, B., Zelaya, F., et al. (2008). Decomposing the neural correlates of antisaccade eye movements using event-related FMRI. *Cerebral Cortex, 18,* 1148–59.

Ghajar, J., & Ivry, R. B. (2008). The predictive brain state: Timing deficiency in traumatic brain injury? *Neurorehabilitation and Neural Repair, 22,* 217–27.

Gordon, W. A., Haddad, L., Brown, M., Hibbard, M. R., & Sliwinski, M. (2000). The sensitivity and specificity of self-reported symptoms in individuals with traumatic brain injury. *Brain Injury, 14,* 21–33.

Grönqvist, H., Gredebäck, G., & Hofsten, C. (2006). Developmental asymmetries between horizontal and vertical tracking. *Vision Research, 46,* 1754–61.

Heide, W., Kurzidim, K., & Kömpf, D. (1996). Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain, 119,* 1951–69.

Heitger, M. H., Jones, R. D., Macleod, A. D., Snell, D. L., Frampton, C. M., & Anderson, T. J. (2009). Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. *Brain, 132,* 2850–70.

Holzman, P. S., Levy, D. L., & Proctor, L. R. (1976). Smooth pursuit eye movements, attention, and schizophrenia. *Archives of General Psychiatry, 33,* 1415–20.

Hwang, K., Velanova, K., & Luna, B. (2010). Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: A functional magnetic resonance imaging effective connectivity study. *Journal of Neuroscience, 30,* 15535–45.

Iacono, W. G., & Lykken, D. T. (1979). Eye tracking and psychopathology. New procedures applied to a sample of normal monozygotic twins. *Archives of General Psychiatry, 36,* 1361–9.

Keating, E. G. (1991). Frontal eye field lesions impair predictive and visually-guided pursuit eye movements. *Experimental Brain Research, 86,* 311–23.

Khan, A. Z., Lefèvre, P., Heinen, S. J., & Blohm, G. (2010). The default allocation of attention is broadly ahead of smooth pursuit. *Journal of Vision, 10,* 7.

Kowler, E. (2011). Eye movements: The past 25 years. *Vision Research, 51,* 1457–83.

Krauzlis, R. J. (2005). The control of voluntary eye movements: New perspectives. *The Neuroscientist, 11,* 124–37.

Lekwuwa, G. U., & Barnes, G. R. (1996a). Cerebral control of eye movements. I. The relationship between cerebral lesion sites and smooth pursuit deficits. *Brain, 119,* 473–90.

Lekwuwa, G. U., & Barnes, G. R. (1996b). Cerebral control of eye movements. II. Timing of anticipatory eye movements, predictive pursuit and phase errors in focal cerebral lesions. *Brain, 119,* 491–505.

Lipton, R. B., Levin, S., & Holzman, P. S. (1980). Horizontal and vertical pursuit eye movements, the oculocephalic reflex, and the functional psychoses. *Psychiatry Research, 3,* 193–203.

Lisberger, S. G. (2010). Visual guidance of smooth-pursuit eye movements: Sensation, action, and what happens in between. *Neuron, 66,* 477–91.

Lovejoy, L. P., Fowler, G. A., & Krauzlis, R. J. (2009). Spatial allocation of attention during smooth pursuit eye movements. *Vision Research, 49,* 1275–85.

Maruta, J., Lee, S. W., Jacobs, E. F., & Ghajar, J. (2010a). A unified science of concussion. *Annals of the New York Academy of Sciences, 1208,* 58–66.

Maruta, J., Suh, M., Niogi, S. N., Mukherjee, P., & Ghajar, J. (2010b). Visual tracking synchronization as a metric for concussion screening. *The Journal of Head Trauma Rehabilitation, 25,* 293–305.

Morrow, M. J., & Sharpe, J. A. (1995). Deficits of smooth-pursuit eye movement after unilateral frontal lobe lesions. *Annals of Neurology, 37,* 443–451.

Munoz, D. P., & Everling, S. (2004). Look away: The anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5,* 218–28.

Orban de Xivry, J. J., & Lefevre, P. (2009). Interactions between saccades and pursuit. In L. R. Squire (Ed.), *Encyclopedia of Neuroscience* (pp. 421–428). Oxford: Academic Press.

Osborne, L. C., Lisberger, S. G., & Bialek, W. (2005). A sensory source for motor variation. *Nature, 437,* 412–6.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1,* 385–401.

Rashbass, C. (1961). The relationship between saccadic and smooth tracking eye movements. *The Journal of Physiology, 159,* 326–38.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). 'Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia, 35,* 747–758.

Rothenberg, S. J., & Selkoe, D. (1981). Specific oculomotor deficit after diazepam. II. Smooth pursuit eye movements. *Psychopharmacology (Berl), 74,* 237–40.

Rottach, K. G., Zivotofsky, A. Z., Das, V. E., Averbuch-Heller, L., Discenna, A. O., Poonyathalang, A., et al. (1996). Comparison of horizontal, vertical and diagonal smooth pursuit eye movements in normal human subjects. *Vision Research, 36,* 2189–95.

Shagass, C., Roemer, R. A., & Amadeo, M. (1976). Eye-tracking performance and engagement of attention. *Archives of General Psychiatry, 33,* 121–5.

Simpson, J. I., & Graf, W. (1981). Eye-muscle geometry and compensatory eye movements in lateral-eyed and frontal-eyed animals. *Annals of the New York Academy of Sciences, 374,* 20–30.

Stuss, D. T., Stethem, L. L., Hugenholtz, H., Picton, T., Pivik, J., & Richard, M. T. (1989). Reaction time after head injury: Fatigue, divided and focused attention, and consistency of performance. *Journal of Neurology, Neurosurgery & Psychiatry, 52,* 742–728.

Umeda, Y., & Sakata, E. (1975). The circular eye-tracking test. I. Simultaneous recording of the horizontal and vertical component of eye movement in the eye-tracking test. *ORL Journal for Oto-Rhino-Laryngology and its Related Specialties, 37,* 290–8.

van der Steen, J., Tamminga, E. P., & Collewijn, H. (1983). A comparison of oculomotor pursuit of a target in circular real, beta or sigma motion. *Vision Research, 23,* 1655–61.

Van Donkelaar, P., & Drew, A. S. (2002). The allocation of attention during smooth pursuit eye movements. *Progress in Brain Research, 140,* 267–77.

Van Gelder, P., Lebedev, S., Liu, P. M., & Tsui, W. H. (1995). Anticipatory saccades in smooth pursuit: Task effects and pursuit vector after saccades. *Vision Research, 35,* 667–78.

Wang, P., & Nikolić, D. (2011). An LCD Monitor with sufficiently precise timing for tesearch in vision. *Frontiers in Human Neuroscience, 5,* 85.

Westheimer, G. (1954). Mechanism of saccadic eye movements. *A.M.A. Archives of Ophthalmology, 52,* 710–24.

White, O. B., Saint-Cyr, J. A., Tomlinson, R. D., & Sharpe, J. A. (1983). Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. *Brain, 106,* 571–87.

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RESEARCH ARTICLE

Adaptation of visual tracking synchronization after one night of sleep deprivation

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Abstract The temporal delay between sensory input and motor execution is a fundamental constraint in interactions with the environment. Predicting the temporal course of a stimulus and dynamically synchronizing the required action with the stimulus are critical for offsetting this constraint, and this prediction–synchronization capacity can be tested using visual tracking of a target with predictable motion. Although the role of temporal prediction in visual tracking is assumed, little is known of how internal predictions interact with the behavioral outcome or how changes in the cognitive state influence such interaction. We quantified and compared the predictive visual tracking performance of military volunteers before and after one night of sleep deprivation. The moment-to-moment synchronization of visual tracking during sleep deprivation deteriorated with sensitivity changes greater than 40 %. However, increased anticipatory saccades maintained the overall temporal accuracy with near zero phase error. Results suggest that acute sleep deprivation induces instability in visuomotor prediction, but there is compensatory visuomotor adaptation. Detection of these visual tracking features may aid in the identification of insufficient sleep.

Keywords Eye movement · Attention · Fatigue · Smooth pursuit · Visuomotor · Screening · Sleepiness

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Introduction

Predicting the temporal course of a stimulus and dynamically synchronizing the required action with the stimulus constitute a critical ability for offsetting the temporal delay between sensory input and motor execution. This ability to predict timing is regarded as a function of attention (Ghajar and Ivry 2009). The oculomotor system provides an ideal model for studying the processes involved in sensorimotor synchronization because gaze orientation reflects attention (Baumann and Greenlee 2009; Chen et al. 2002; Corbetta et al. 1998; de Hann et al. 2008; Khan et al. 2010; Schluppeck et al. 2005; Silver et al. 2005; Spering and Carrasco 2012) and eye movements can be precisely and objectively recorded. The visuomotor synchronization process may be best studied using tracking of a target with a predictable motion pattern, such as in a sinusoidal motion, wherein the target can be locked on the fovea without a significant overall phase lag (Stark et al. 1962; Westheimer 1954). The accuracy of visual tracking belies the reaction delay known for smooth pursuit initiation and maintenance (Rashbass 1961; Tavassoli and Ringach 2009).

During visual tracking, a moment-to-moment (or dynamic) synchronization of the gaze and the target is maintained and fine-tuned by a synergy of saccade and smooth pursuit eye movements. Most of the saccades are forward driving, and when the target movement is

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predictable, they can be classified into two categories, catch-up and anticipatory. A catch-up saccade originates behind the target and reduces the phase lag to bring the gaze onto the moving target. The frequency of catch-up saccades increases during pursuit when the target trajectory is unpredictable or when the smooth pursuit gain decreases (Collewijn and Tamminga 1984; Friedman et al. 1991). However, unlike catch-up saccades, an anticipatory saccade takes the gaze away from the target to a predicted future target position and can be intrusive to the gaze–target synchronization. The occurrence of anticipatory saccades may be facilitated by attention paid to tracking rather than to the target (Van Gelder et al. 1995).

Smooth pursuit and saccade eye movements are subserved by complex neural networks involving many cortical and subcortical regions (Krauzlis 2004; Lencer and Trillenberg 2008; Orban de Xivry and Lefevre 2009), and synchronization between the gaze and a moving target can be influenced by various pathological factors affecting these neural sites. One such condition is sleep deprivation, a common problem in modern society that alters the neural activity in a wide range of brain regions, many of which are involved in oculomotor control (Chee et al. 2011; Gazes et al. 2012; Poudel et al. 2009; Tomasi et al. 2009). Sleep deprivation or a sudden inversion of the day–night shift degrades performance in visual tracking and saccadic tasks, suggesting that oculomotor performance may be used for monitoring sleepiness (De Gennaro et al. 2000; Fransson et al. 2008; Porcu et al. 1998).

Despite indications of visual tracking degradations associated with sleepiness, the dynamics of gaze−target synchronization under sleep deprivation are still not understood. It is known that sleep deprivation reduces smooth pursuit velocity gain but does not alter the overall phase relationship between the gaze and the target (De Gennaro et al. 2000); however, the mechanism that compensates for a possible accumulation of phase lag caused by insufficient smooth pursuit velocity is not clear. In addition, the dynamics of visual tracking during sleepiness have not been described in sufficient detail. The parameters used in previous studies, such as smooth pursuit gain and mean phase, are appropriate for describing overall performance but do not characterize moment-to-moment oculomotor dynamics. Finally, the influence of saccades on gaze–target relationships during sleep deprivation has received little attention.

The main purpose of this study is to investigate the changes in dynamic visuomotor synchronization after acute sleep deprivation. We utilized a continuous visual tracking paradigm with the target moving along a circular trajectory at a constant speed. While the target motion is highly predictable in this paradigm, the neural computations required for dynamic coordination of two-dimensional eye movements are complex and subject to degradation under sleep deprivation conditions. We hypothesize that visuomotor adaptation, which optimizes synchronization during sleep deprivation, can be detected using spatial and temporal predictive visual tracking parameters.

Methods

Subjects

A total of 97 military volunteers were enrolled in the study at the United States Army Research Institute of Environmental Medicine (USARIEM) located at the Natick Soldier Center, Natick, MA. The enrollment inclusion criteria were men or women 18–50 years of age, who had completed at least 12 years of education. The exclusion criteria were as follows: prior history of head injury with loss of consciousness, substance abuse problems/treatment, known neurological disorders, major psychiatric disorders (including attention deficit hyperactivity disorder), vision worse than 20/30 after correction, and hearing problems. Family history of psychiatric disorders was not assessed.

Of the 97 subjects, two were screened out for a possible previous head injury, and eight were excluded due to scheduling conflicts. Data were collected from the remaining 87 subjects (68 males, 19 females, mean age $= 21.8 \pm 3.7$ years). The protocol was reviewed and approved by the USARIEM Human Use Review Committee and the USARIEM Office of Research Quality and Compliance. Written informed consent was obtained from all participants prior to data collection.

Testing time arrangement

Three measurements of visual tracking performance were taken during the required 26 h period of sustained wakefulness. All subjects were billeted on post. Sleep on the night preceding the study was as per normal habit with morning formation starting at 0630. The baseline measurement (Time 1) took place between 0630 and 0930, which coincides with the subjects' typical morning schedules. The second measurement (Time 2) was at predawn between 0200 and 0400, and the last measurement (Time 3) was again in the morning between 0630 and 0930 in order to control for the effects of circadian rhythm. During the experimental period, the subjects engaged in ordinary activities, including mild to moderate physical activity (walking, treadmill). Caffeine consumption was not permitted during this period. A member of the research team or a member of the soldiers' chain of command accompanied the subjects throughout the entire experimental period to ensure wakefulness.

Testing procedure

Details of the testing setup are described in a previous publication (Maruta et al. 2013). Testing was conducted in a well-illuminated room without a window to the outside. The visual stimulus was presented on a 22″ LCD monitor running at 120 Hz frame rate (Samsung SyncMaster 2233RZ, see Wang and Nikolić 2011). The subject sat in front of the LCD screen at a distance of 47.5 cm with the head stabilized by a head- and chin-rest during testing. Eye movements were monitored binocularly with a desktop camera operating at a sampling rate of 500 Hz, and horizontal and vertical positions of the gaze and the target were recorded (EyeLink 1000, SR Research, Ontario, Canada, spatial resolution 0.01° root-mean-square error).

The visual target was a red circular target, 0.5° diameter in visual angle with a 0.2° black dot in the center, presented on the black background. Each visual tracking trial was preceded and succeeded by a period of central fixation. When the initial fixation was detected, the target jumped upward from the center by 10° and moved clockwise along a circular trajectory of 10° radius. The frequency of the target motion was 0.4 Hz, which was equivalent to the target having a tangential speed of 25°/s. After six cycles of movement, the target jumped back to the center. Two identical trials were given consecutively.

Eye movement analysis

Initial data processing and detection of saccade

Eye movement data were analyzed by means of custom MATLAB programs (Matlab R2011b, the MathWorks, Natick, MA, USA). Blinks and other periods of pupil occlusion in the data were detected by the computer program and were excluded from further analyses. The data from the first stimulus cycle were not analyzed since the segment contained the initial transient response to the target movement. A precaution was taken to detect and remove artifacts caused by possible head drift during tests by linearly interpolating the offset in the gaze fixation data before and after circular tracking. Horizontal and vertical eye velocities were computed by two-point differentiating the position data and smoothed by means of a two-sided exponential filter with inverse of the time constant set at 167 Hz. The absolute instantaneous eye speed was calculated as the magnitude of the vector sum of the filtered horizontal and vertical velocities. The filtered horizontal and vertical eye velocity data were differentiated to obtain horizontal and vertical accelerations, which were further smoothed with the same two-sided exponential filter. The absolute instantaneous acceleration was then computed from vector summation of horizontal and vertical accelerations, which was used in the first step of saccade detection strategy described below. Unfiltered horizontal and vertical velocities were used for calculating the velocities in the parallel (tangential) and perpendicular (radial) directions of the circular motion, which were further processed after saccade detection.

Events of saccadic and smooth pursuit components of visual tracking were identified using a modification of an algorithm with adaptive thresholds for local acceleration and velocity (Behrens et al. 2010; Nyström and Holmqvist 2010). An approach with adaptive thresholds was preferred to one with a fixed threshold because large individual variations in smooth pursuit gain were expected (Maruta et al. 2013) and because a precise isolation of smooth pursuit from saccades was desired. In the first step of the algorithm, a local acceleration threshold was estimated from the local variation of acceleration values within a 50 ms sliding window. Within each sliding window, the mean and standard deviation (σ_{acc}) of the acceleration values were calculated. The threshold for saccade detection was set to be the acceleration value of 5 σ_{acc} above the mean of the immediately preceding window. This threshold was frozen until the end of the saccade was detected in the following manner. As the eye accelerates and decelerates during a saccade, the absolute acceleration forms two peaks. Based on this fact, the end of a suspected saccade was marked when the absolute acceleration value fell below the frozen threshold after the second peak. At this point, the threshold was unfrozen to detect the next saccade candidate. We set the minimum interval between the end of a saccade and the beginning of the next saccade to be 20 ms. Any adjacent pair of probable saccades occurring within a shorter interval were combined as a single saccade.

In the second step of the algorithm, velocity thresholds were determined locally and adaptively to refine the onset and offset of each saccade. Within the absolute velocity data of the 20 ms intervals before and after each saccade detected in the first step, the mean (μ_{vel}) and standard deviation (σ_{vel}) were calculated, and a threshold value corresponding to $\mu_{vel} + \sigma_{vel}$ was determined. Starting from the point corresponding to the highest velocity within each saccade segment, the point where eye velocity first exceeded the threshold was searched backward and was marked as the onset of the saccade. Similarly, starting from the point corresponding to the highest velocity, the point where eye velocity first fell below the threshold was searched forward and was marked as the end of the saccade. Both horizontal and vertical eye velocities were processed in this manner, and the duration of each saccade was determined as the time period that covered the saccade detected in both the horizontal and vertical traces. The minimum duration of a saccade set by the computer program was 6 ms. The smallest amplitude of the detected saccades was near 0.1°. The

detected saccades were registered with the filtered horizontal and vertical eye velocities, from which desaccaded velocity traces were generated by replacing the saccade segments with straight lines connecting the ends of smooth pursuit velocity segments to create continuous profiles of smooth pursuit velocity modulations. The detected saccades were also registered with tangential and radial eye velocities and removed from data representation. The tangential and radial smooth pursuit velocities were filtered with an 11-order finite impulse response (FIR) low-pass filter with cutoff frequency at 100 Hz, which further removed 5 points (10 ms) before and after each saccade.

Parameters for visual tracking performance

The overall central tendencies of visual tracking performance were evaluated with four parameters. *Mean phase error* was calculated as the average angular difference between the gaze and the target relative to the origin of the circular trajectory of the target, with a positive phase error indicating the gaze leading the target. Phase error is a spatial manifestation of instantaneous temporal error. Mean phase error, measured in phase angle, describes the overall spatio-temporal accuracy. *Mean radial error*, measured in visual angle, was calculated as the average deviation of the gaze position from the circular trajectory of the target, with a negative value indicating a tendency for the gaze to fall inside the circle with a 10° radius. *Horizontal* and *vertical gains* (H and V gains) were calculated as the ratios of the amplitudes of smooth pursuit eye velocity to the target velocity in the horizontal and vertical directions, respectively. The amplitudes of horizontal and vertical smooth pursuit velocity modulations were obtained by fitting desaccaded eye velocity traces with sine curves of the frequency of the circular movement of the target (0.4 Hz) using fast Fourier transformation. Sluggish eye movements have a gain value less than 1. *Tangential gain* was calculated as the ratio of average tangential smooth pursuit velocity to the target tangential velocity.

The synchronization dynamics were first quantified with parameters related to eye position changes as described in our previous papers (Maruta et al. 2010, 2013). Gaze position errors measured in visual angle were projected onto the tangential direction of the target trajectory (tangential error) and the orthogonal direction (radial error). The tangential error is proportional to the phase error of the gaze, and the positive value represents the eye position leading the target. *The standard deviation of tangential error* (SDTE) and *standard deviation of radial error* (SDRE) measured the positional variability along the tangential and radial directions, respectively. The smaller the SDTE or SDRE, the more stable the tracking.

In this paper, we introduce two novel parameters to capture the velocity dynamics of visual tracking, *average powers of radial* and *tangential velocities* (APRV and APTV), representing fluctuations of smooth pursuit velocity in the radial and tangential directions of the circular motion. The power spectral densities (PSD) of the velocity components were estimated using the *psd* command with Welch estimator in Matlab R2011b. Specifically, desaccaded velocity traces were broken into Hamming windowed segments of 500 ms with a 250 ms overlap, and the final PSD was the average of PSDs of these segments. APRV and APTV were calculated as the integral of the PSD over the 5 and 30 Hz temporal frequency band. This frequency band was chosen to avoid the interference from frequency of the target movement while extracting the information related to eye velocity fluctuations. The upper frequency limit corresponds to the upper range of the frequency with which extraocular muscles can respond faithfully to isolated signals (Asmussen and Gaunitz 1981; Barmack et al. 1971). The FIR low-pass filter reduced the signal by less than 1.5 % within this frequency range. A large power value indicates high-frequency fluctuations of smooth pursuit, i.e., tracking instability.

Saccade properties

Saccades were classified into three categories based on the relationship between the gaze and target positions before and after their occurrences: (1) catch-up saccades, (2) anticipatory saccades, and (3) others. Both catch-up and anticipatory saccades are phase advancing. In this study, catch-up saccades were defined as those that had the initial gaze position behind the target and reduced the lag, but did not generate a phase lead larger than the initial lag. Thus, the mid-point of a catch-up saccade was behind the target. Anticipatory saccades were defined as those with the final gaze position leading the target by more than the initial phase lag. Thus, the mid-point of an anticipatory saccade was ahead of the target. The third category of saccades included backward saccades and those that shifted the gaze strictly in the radial direction. Saccades in this category were rare and were not analyzed in this study. For each saccade the *amplitude* (which is defined as the differences in eye positions at the onset and offset of the saccade) and *peak velocity* were recorded. The *saccade rate*, defined as the number of saccades per cycle, was also recorded for each type of saccades. To test whether there was an amplitude-dependent rate change, catch-up and anticipatory saccades were classified as small or large based on the median saccade amplitudes from the baseline test.

Statistical analysis

The parameters for smooth pursuit and saccadic eye movements were evaluated for each eye separately, and

the measures from the eye with the smaller SDRE scores were used in the statistical analyses (Maruta et al. 2013). A mixed effects model, which is suitable for detecting subject-level pattern of change and robust to non-normally distributed data, was contrasted by SPSS (version 20) to examine the changes in visual tracking performance during sustained wakefulness at three time points of measurements. All tests were evaluated at a 0.05 significance level. When a significant change was detected, parameter comparison was conducted to explore specific changes among sleep deprivation time points.

To test the effect of sleep deprivation on the relationship between saccade peak velocity and amplitude, the data were logarithmically transformed and a mixed linear model was constructed with intra-individual factors taken into account. The Wald test was applied to the slopes of relationships at different sleep deprivation time points.

Results

Changes in tracking performance

Typical single-subject examples of circular tracking eye movements are shown in Fig. 1. The left and right columns represent visual tracking before and after one night of sleep deprivation, respectively. Compared to baseline, the tracking performance after one night of sleep deprivation had larger spatial (Fig. 1a vs. b) and spatio-temporal positional variability (Fig. 1c vs. d) and larger high-frequency fluctuations in smooth pursuit velocity (Fig. 1e vs. f). In contrast, no significant peak shift of the distribution of the spatio-temporal errors was observed after one night of sleep deprivation (Fig. 1c vs. d).

Changes in overall performance

In a group analysis, we confirmed that smooth pursuit velocity gain was reduced during sleep deprivation (Fig. 2c, d). The reduction during sleep deprivation was significant in both horizontal ($F(2, 86) = 16.02$, $p < 0.0001$) and vertical gains ($F(2, 86) = 4.64$, $p = 0.01244$), as well as the average tangential gain during sleep deprivation ($F(2, 86) = 16.8$, $p < 0.0001$). A significant change was not observed in the mean phase error (Fig. 2a, $F(2, 86) = 0.78$, $p = 0.464$), i.e., the reduced smooth pursuit velocity during sleep deprivation did not result in accumulation of spatio-temporal lag. The reduction in smooth pursuit velocity gain was also not accompanied by a change in the mean radial error (Fig. 2b, $F(2, 86) = 0.85$, $p = 0.43$). Thus, the maintenance of accurate phase despite the reduction in smooth pursuit velocity gain was not achieved by a reduction in the amplitude of gaze excursion.

Changes in dynamic performance

The stability of the gaze position relative to the target was reduced during sleep deprivation. On average, the increase in SDTE was from 0.78 at Time 1 to 1.26 at Time 3 (Fig. 2e, $F(2, 86) = 13.40$, $p < 0.0001$), and the increase in SDRE was from 0.5 at Time 1 to 0.73 at Time 3 (Fig. 2f, $F(2, 86) = 12.69$, $p < 0.0001$). The stability of tangential velocity was also significantly reduced (Fig. 2g, $F(2, 86) = 6.68$, $p = 0.002$), although not radial velocity (Fig. 2h, $F(2, 86) = 0.69$, $p = 0.504$). Thus, on the whole, sleep deprivation degraded the moment-to-moment synchronization between the gaze and the target.

Changes in saccade properties

Figure 3 shows the relationships between saccade peak velocities and saccade amplitudes, i.e., main sequences, of catch-up and anticipatory saccades. The data from all subjects were combined so that each point in the graphs represents an individual saccade. There was a strong dependence of saccade peak velocities on saccade amplitudes at all time points. The slopes of the main sequences at three time points were significantly different for both catch-up and anticipatory saccades (Wald chi-square = 71.48, $p < 0.0001$), and the contrast analysis indicated a monotonical decline of slope during sleep deprivation (Time 1 vs. Time 2, $p < 0.0001$; Time 1 vs. Time 3, $p < 0.0001$; Time 2 vs. Time 3, $p < 0.001$). No significant difference was detected between the pattern of changes in catch-up and anticipatory saccades (Quasi Likelihood under independence model = 344.50, $p = 0.19$).

The effect of sleep deprivation on saccade amplitudes and rates was examined next. The group average of median amplitudes of catch-up saccades was 0.94°, and there was no significant change during sleep deprivation (Fig. 4a, $F(2, 86) = 0.10$, $p = 0.90$). On the other hand, the group average of the median amplitudes of anticipatory saccades significantly changed during sleep deprivation (Fig. 4b, $F(2, 79.80) = 10.28$, $p < 0.0001$) and decreased from 1.4° at Time 1 to 1.1° at Time 3. The rates of catch-up saccades were approximately 5 per cycle, and there was no significant change during sleep deprivation ($F(2,321.60) = 0.02$, $p = 0.98$), but the rates of anticipatory saccades changed significantly ($F(2, 316.07) = 6.74$, $p = 0.001$) and increased from 1.5 per cycle to 2.5 per cycle.

There was no significant pair-wise difference among the three testing times in the rate of small ($p > 0.48$) or large ($p > 0.25$) catch-up saccades or large anticipatory ($p > 0.25$) saccades. In contrast, the rate of small anticipatory saccades significantly increased during sleep deprivation compared with baseline measurement ($p < 0.0001$ at T1 vs. T2, and T1 vs. T3, Fig. 4d).

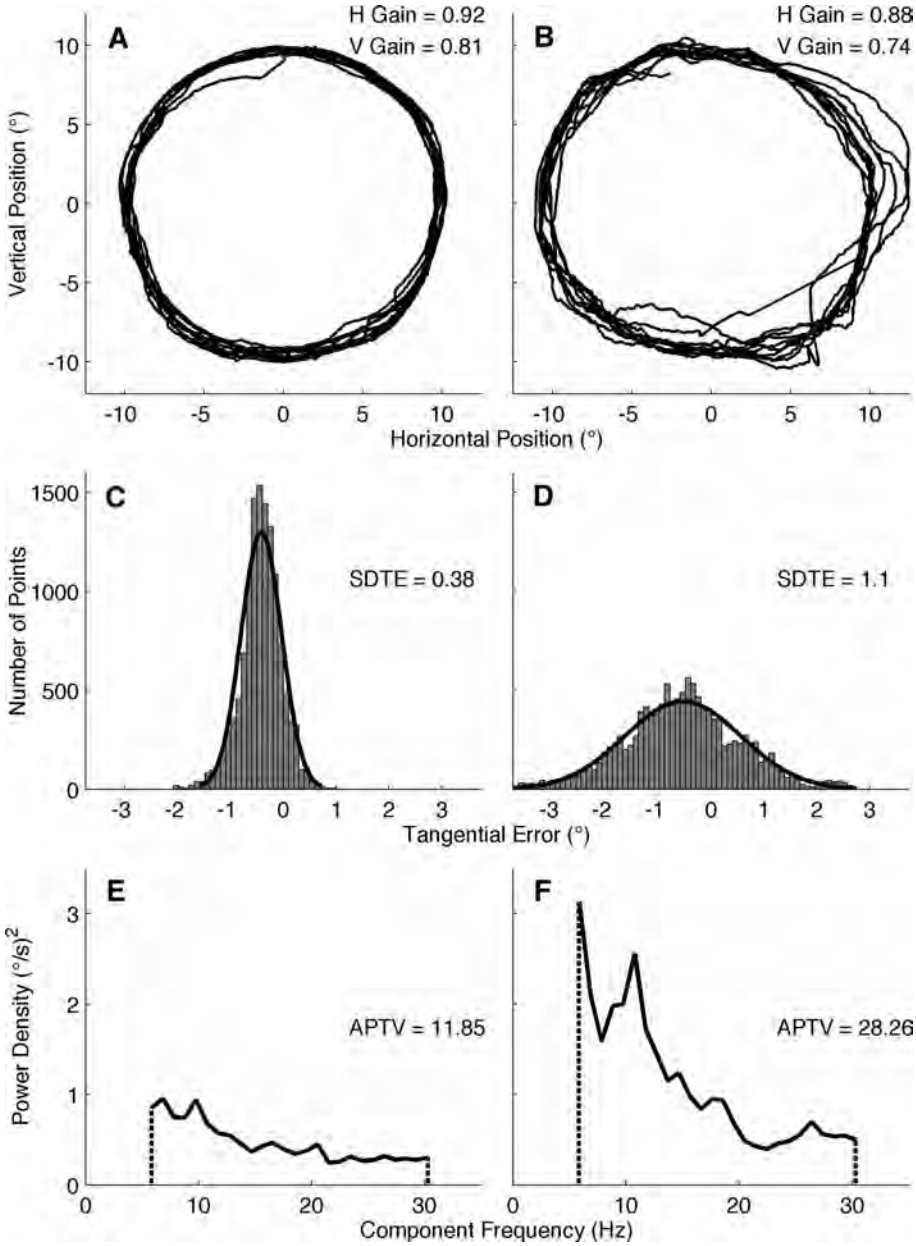

Fig. 1 Characterization of circular visual tracking from a single subject before (Time 1, *left column*) and after (Time 3, *right column*) one night of sleep deprivation. **a**, **b** Two-dimensional gaze trajectories. *Horizontal* and *vertical* smooth pursuit velocity gain values are shown in the *inset*. **c**, **d** Histograms of tangential errors. Positive values indicate the gaze ahead of the target. The standard deviation of the distribution (SDTE) is shown in the *inset*. **e**, **f** Power density function of tangential eye velocity between 5 and 30 Hz. The average powers calculated as the areas under the curves are shown in the *inset*

Smooth pursuit–saccade interaction

Generally, an anticipatory saccade results in a transient reduction in the velocity gain of the immediate smooth pursuit (see example in Fig. 5a, shaded area). Thus, the increase in rate of anticipatory saccades could have contributed to the reduced smooth pursuit velocity gain. Alternatively, given that a correct phase relationship between the gaze and the target was maintained, anticipatory saccades could have been triggered to compensate for the reduced smooth pursuit gain and the consequent phase lag. We tested whether the reduced smooth pursuit velocity gain was a direct result of the increased rate of anticipatory saccades. Here, modulations of instantaneous gain were expressed in terms of the velocity component in the tangential direction, and the average gain was calculated for the data that excluded smooth pursuit segments that immediately followed an anticipatory saccade (Fig. 5a, shaded area). The change during sleep deprivation in the average gain of the remaining segments was still significant (Fig. 5b, $F(2, 86) = 16.53$, $p = 0.0001$).

Discussion

In this study, we confirmed findings from previous studies (De Gennaro et al. 2000; Fransson et al. 2008; Porcu et al.

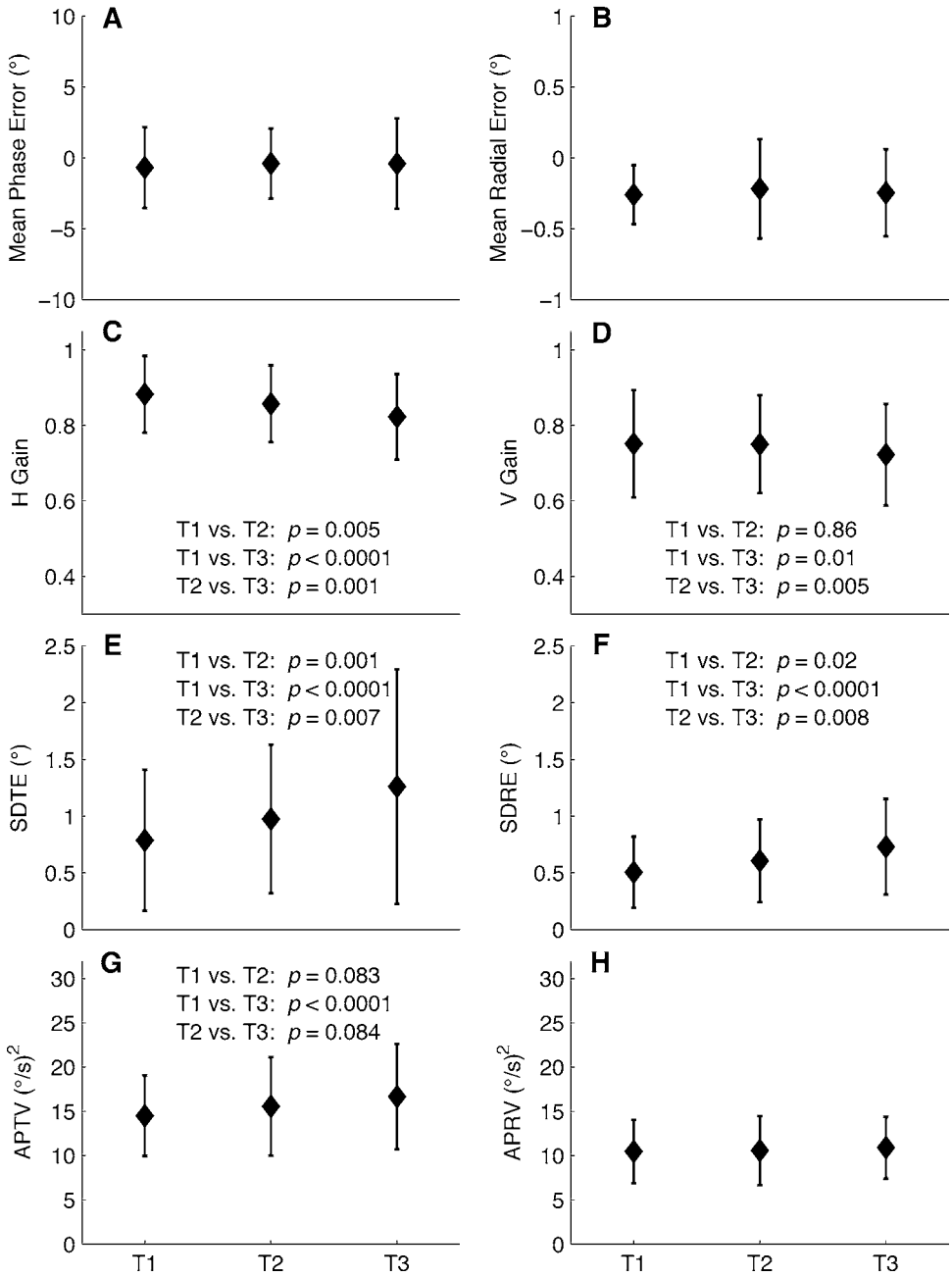

Fig. 2 Effect of sleep deprivation on visual tracking performance. The average scores of each parameter across subjects are plotted against testing times. T1, T2, and T3 indicate measurements at baseline, predawn, and next morning, respectively. The *error bars* denote one standard deviation across subjects. Shown in *insets* are *p* values for tests within the linear mixed model with a significant difference across testing times. **a** Mean phase error. **b** Mean radial error. **c** Horizontal gain. **d** Vertical gain. **e** Standard deviation of tangential gaze error. **f** Standard deviation of radial gaze error. **g** Power of tangential velocity between 5 and 30 Hz. **h** Power of radial velocity between 5 and 30 Hz

1998) indicating that acute sleep deprivation degrades predictive visual tracking in the form of reduced smooth pursuit velocity gain but without changing the overall spatiotemporal relationship between the gaze and the moving target. Our results suggest that under sleep deprivation, visuomotor prediction is less precise; however, predictive mechanisms remain engaged and adapt to the sleep deprivation-induced performance instability by increasing anticipatory saccades. Furthermore, we found small but significant changes in tracking behavior as early as 20–22 h of wakefulness using a continuous two-dimensional tracking paradigm.

Since visual tracking requires both low-level sensorimotor and high-level cognitive functions, sleep deprivation-induced deterioration of dynamic synchronization may stem from deficits in neural circuits that support either functions. However, increased high-frequency components of smooth pursuit velocity that are unrelated to the target motion and decreased peak velocity of saccades during sleep deprivation likely indicate deficits in motor-related neural circuits. Saccades made in response to step-wise movement of fixation points during sleep deprivation have reduced peak velocity (De Gennaro et al. 2000; Fransson et al. 2008; Goldich

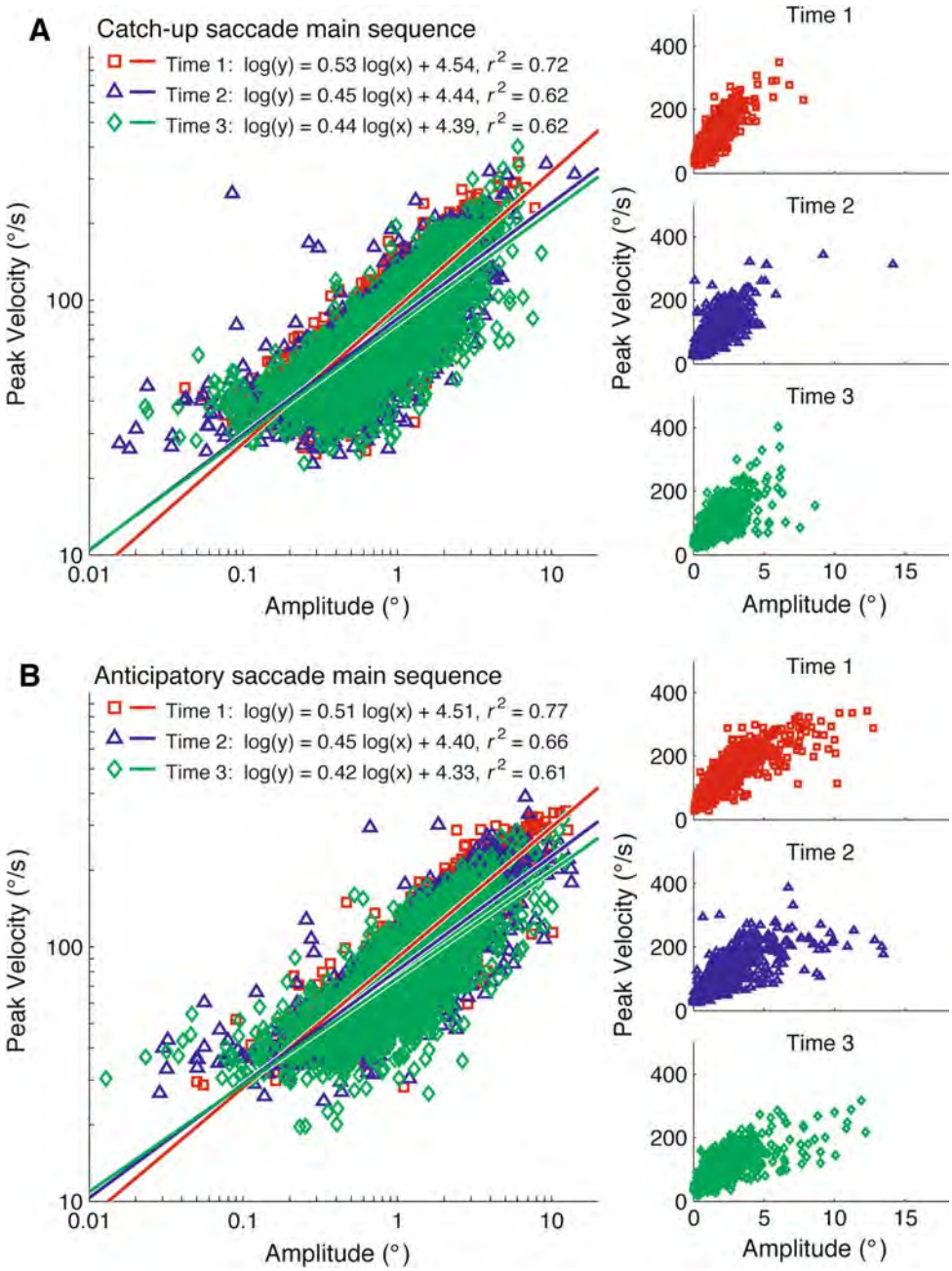

Fig. 3 Main sequences for **a** catch-up saccades and **b** anticipatory saccades for the three testing times after logarithmic transformation. The main sequence for each testing time before logarithmic transformation shown separately in the *right column*

et al. 2010; Porcu et al. 1998; Russo et al. 2003; Zils et al. 2005; but see Bocca and Denise 2006), which has been attributed to reduced motor commands in parietal lobes, basal ganglia, thalamus, cerebellum, and midbrain (Russo et al. 2003; Thomas et al. 2000). These regions are also involved in the regulation of smooth pursuit eye movement (Konen and Kastner 2008; Mustari et al. 2009; Tanaka 2005; Yoshida and Tanaka 2009). In addition, the variation in visual tracking during sleep deprivation has been correlated with motion-sensitive cortical regions (Chee et al. 2011; Osborne et al. 2005). Reduced neural activity in these regions during sleep deprivation may lower the signal-to-noise ratio, causing tracking to be less precise. Similarly, reduced smooth pursuit velocity gain is likely a result of reduced sensorimotor functioning.

The involvement of cognitive processes in visual tracking is evident based on recent studies (see review by Barnes 2008). Within cortical association regions related to visual tracking, the frontal lobe plays a critical role in predictive timing (Coppe et al. 2012). Abnormal activity in the cortical frontal regions during sleep deprivation may be detected as reduced peak oxyhemoglobin level (Miyata et al. 2010), reduced metabolism (Wu et al. 2006), or increased power

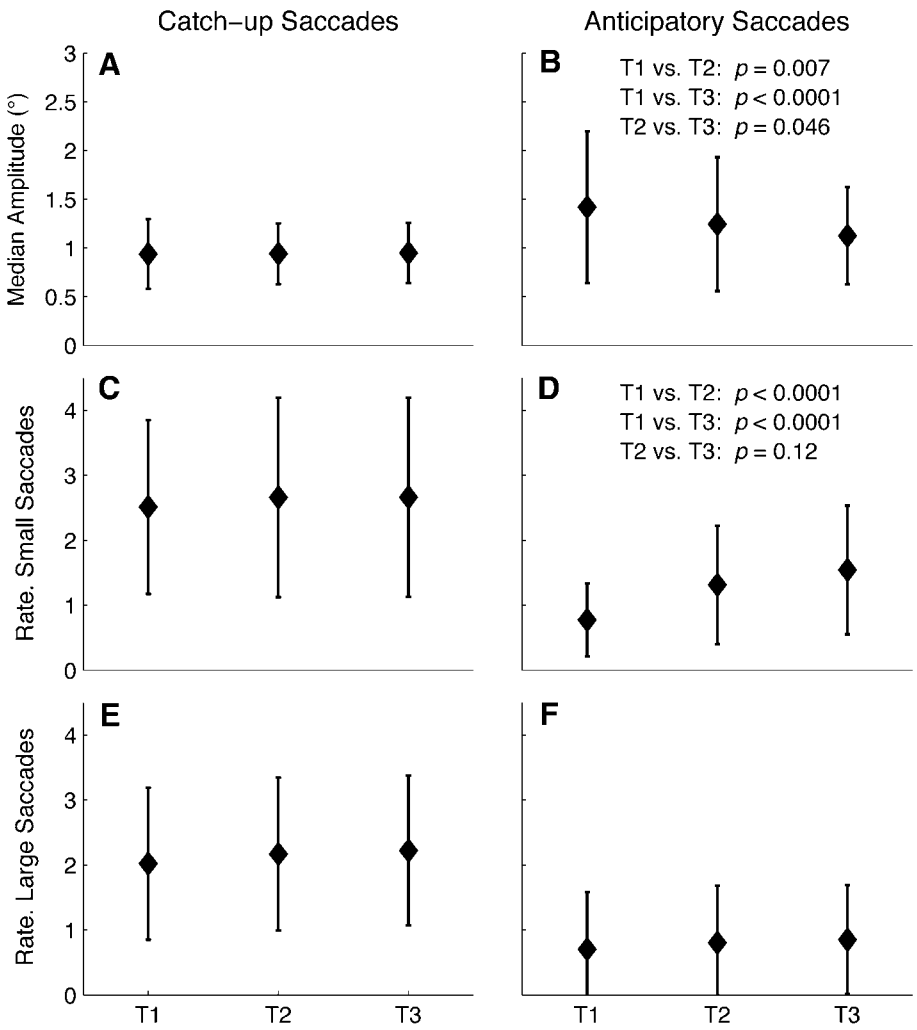

Fig. 4 Changes in amplitudes and rates of catch-up saccade (*left column*) and anticipatory saccade (*right column*) during sleep deprivation. The mean values across subjects are plotted against testing times. T1, T2, and T3 indicate measurements at baseline, predawn, and next morning, respectively. The *error bars* denote one standard deviation across subjects. **a**, **b** Median amplitudes. **c**, **d** Average numbers of small saccades per cycle. **e**, **f** Average numbers of large saccades per cycle. Small and large sizes are defined relative to the median amplitude in each saccade category at baseline

of the theta band in electroencephalography (Forest and Godbout 2000). Altered neural activities in the frontal regions may affect predictive visual tracking by variably increasing processing time or incorrectly estimating the target velocity, causing a temporal mismatch between the target and gaze positions.

Despite the reduced smooth pursuit velocity gain, the overall phase of visual tracking remained accurate during sleep deprivation. Although this relationship could be achieved by a reduction in the amplitude of the gaze positional excursion, such as seen in subjects under methadone treatment (Rothenberg et al. 1980), we found that maintenance of accurate phase response during sleep deprivation was achieved by saccades that anticipated the target. Our analysis suggests that it is a reduction in smooth pursuit velocity gain that induces anticipatory saccades, and not vice versa. In order for this effect to occur, the brain must predict that the gaze will fall behind the target and proactively overcompensate the predicted lag. Our analysis further indicates that large phase errors are avoided by increasing the rate of only small anticipatory saccades. Therefore, under acute sleep deprivation, the predictive mechanisms are able to maintain the overall spatiotemporal accuracy by adapting to reduced performance precision.

Neurophysiological changes caused by sleep deprivation may be detected with various oculomotor responses including the latency of pupillary constriction and peak saccade velocity (Goldich et al. 2010; Grace et al. 2010; Rowland et al. 2005; Russo et al. 2003). However, the mean percent change in these parameters is typically less than 10 %. In the present study, we utilized a continuous two-dimensional visual tracking paradigm and showed that the standard deviations of tangential and radial position errors described a 40 % change of moment-to-moment visuomotor synchronization. Given the reliability of the test paradigm (Maruta et al. 2013), detection of these features may better aid in the identification of insufficient sleep.

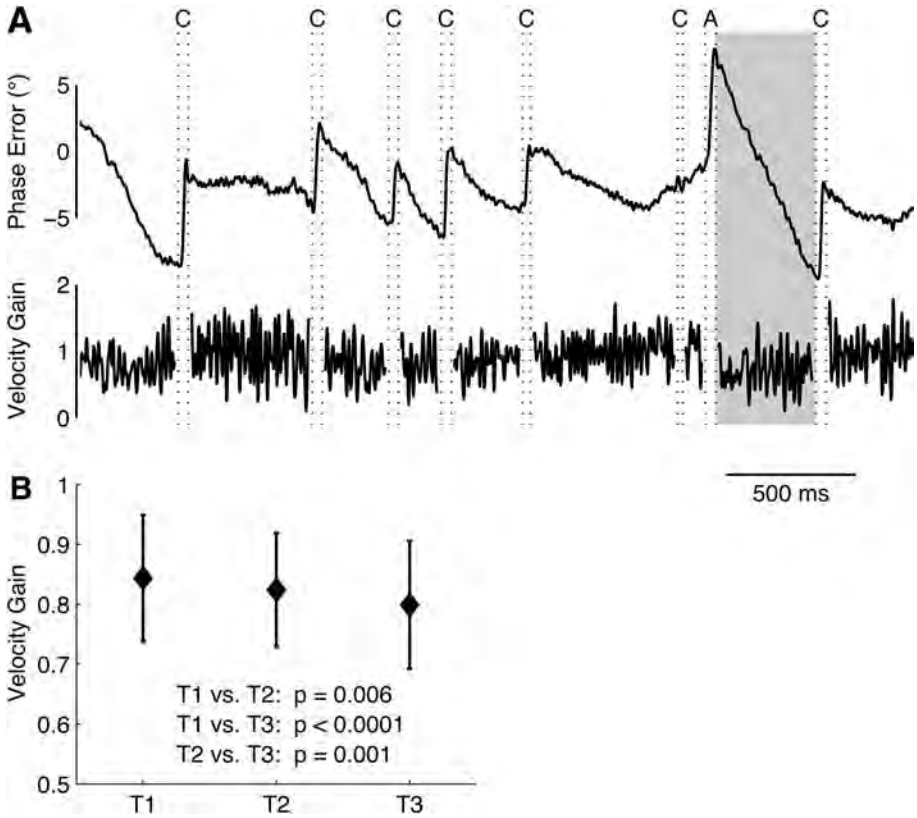

Fig. 5 Effects of anticipatory saccades on smooth pursuit gain. **a** Example from typical baseline testing. The *top trace* shows the phase relationship between the gaze and the target (positive lead). The *bottom trace* shows the modulation of instantaneous smooth pursuit velocity gain in the component parallel to the circular target trajectory, i.e., tangential velocity gain. Catch-up and anticipatory saccades are indicated by *C* and *A*, respectively. Smooth pursuit periods immediately following anticipatory saccades tend to have reduced gains (e.g., the *shaded area*) and were excluded from the analysis shown in **b**. **b** Changes during sleep deprivation in average tangential smooth pursuit velocity gain calculated without the periods after anticipatory saccades. The *error bars* denote one standard deviation across subjects

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Conflict of interest Jamshid Ghajar holds United States patent 7,384,399.

References

Asmussen G, Gaunitz U (1981) Mechanical properties of the isolated inferior oblique muscle of the rabbit. Pflugers Arch 392: 183–190

Barmack NH, Bell CC, Rence BG (1971) Tension and rate of tension development during isometric responses of extraocular muscle. J Neurophysiol 34:1072–1079

Barnes GR (2008) Cognitive processes involved in smooth pursuit eye movements. Brain Cogn 68:309–326

Baumann O, Greenlee MW (2009) Effects of attention to auditory motion on cortical activations during smooth pursuit eye tracking. PLoS ONE 4:e7110

Behrens F, Mackeben M, Schröder-Preikschat W (2010) An improved algorithm for automatic detection of saccades in eye movement data and for calculating saccade parameters. Behav Res Methods 42:701–708

Bocca ML, Denise P (2006) Total sleep deprivation effect on disengagement of spatial attention as assessed by saccadic eye movements. Clin Neurophysiol 117:894–899

Chee MW, Goh CS, Namburi P, Parimal S, Seidl KN, Kastner S (2011) Effects of sleep deprivation on cortical activation during directed attention in the absence and presence of visual stimuli. Neuroimage 58:595–604

Chen Y, Holzman PS, Nakayama K (2002) Visual and cognitive control of attention in smooth pursuit. Prog Brain Res 140:255–265

Collewijn H, Tamminga EP (1984) Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. J Physiol 24:1789–1898

Coppe S, Orban de Xivry JJ, Yüksel D, Ivanoiu A, Lefèvre P (2012) Dramatic impairment due to frontal lobe degeneration. J Neurophysiol 25:293–305

Corbetta M, Akbudak E, Conturo TE, Snyder AZ et al (1998) A common network of functional areas for attention and eye movements. Neuron 21:761–773

De Gennaro L, Ferrara M, Urbani L, Bertini M (2000) Oculomotor impairment after 1 night of total sleep deprivation: a dissociation between measures of speed and accuracy. Clin Neurophysiol 111:1771–1778

de Hann B, Morgan PS, Rorden C (2008) Covert orienting of attention and overt eye movements activate identical brain regions. Brain Res 1204:102–111

Forest G, Godbout R (2000) Effects of sleep deprivation on performance and EEG spectral analysis in young adults. Brain Cogn 43:195–200

Fransson PA, Patel M, Magnusson M, Berg S, Almbladh P, Gomez S (2008) Effects of 24-hour and 36-hour sleep deprivation on smooth pursuit and saccadic eye movements. J Vestib Res 18:209–222

Friedman L, Jesberger JA, Meltzer HY (1991) A model of smooth pursuit performance illustrates the relationship between gain, catch-up saccade rate, and catch-up saccade amplitude in normal controls and patients with schizophrenia. Biol Psychiatry 30:537–556

Gazes Y, Bakitin BC, Steffener J, Habeck C et al (2012) Dual-tasking alleviated sleep deprivation disruption in visuomotor tracking: an fMRI study. Brain Cogn 78:248–256

Ghajar J, Ivry RB (2009) The predictive brain state: asynchrony in disorders of attention? Neuroscientist 15:232–242

Goldich Y, Barkana Y, Pras E, Zadok D et al (2010) The effects of sleep deprivation on oculomotor responses. Curr Eye Res 35:1135–1141

Grace PM, Stanford T, Gentgall M, Rolan PE (2010) Utility of saccadic eye movement analysis as an objective biomarker to detect the sedative interaction between opioids and sleep deprivation in opioid-naïve and opioid-tolerant populations. J Psychopharmacol 24:1631–1640

Khan AZ, Lefèvre P, Heinen SJ, Blohm G (2010) The default allocation of attention is broadly ahead of smooth pursuit. J Vis 10:7

Konen CS, Kastner S (2008) Representation of eye movements and stimulus motion in topographically organized areas of human posterior parietal cortex. J Neurosci 28:8361–8375

Krauzlis RJ (2004) Recasting the smooth pursuit eye movement system. J Neurophysiol 91:591–603

Lencer R, Trillenberg P (2008) Neurophysiology and neuroanatomy of smooth pursuit in humans. Brain Cogn 68:219–228

Maruta J, Suh M, Niogi SN, Mukherjee P, Ghajar J (2010) Visual tracking synchronization as a metric for concussion screening. J Head Trauma Rehabil 25:293–305

Maruta J, Heaton KJ, Kryskow EM, Maule AL, Ghajar J (2013) Dynamic visuomotor synchronization: quantification of predictive timing. Behav Res Methods 45:289–300

Miyata S, Noda A, Ozaki N, Hara Y et al (2010) Insufficient sleep impairs driving performance and cognitive function. Neurosci Lett 469:229–233

Mustari MJ, Ono S, Das VE (2009) Signal processing and distribution in cortical-brainstem pathways for smooth pursuit eye movements. Ann N Y Acad Sci 1164:147–154

Nyström M, Holmqvist K (2010) An adaptive algorithm for fixation, saccade, and glissade detection in eyetracking data. Behav Res Methods 42:188–204

Orban de Xivry J–J, Lefevre P (2009) Interactions between saccades and pursuit. In: Squire LR (ed) Encyclopedia of neuroscience. Academic Press, Oxford

Osborne LC, Lisberger SG, Bialek W (2005) A sensory source for motor variation. Nature 437:412–416

Porcu S, Ferrara M, Urbani L, Bellatreccia A, Casagrande M (1998) Smooth pursuit and saccadic eye movements as possible indicators of nighttime sleepiness. Physiol Behav 65:437–443

Poudel GR, Jones RD, Innes CR, Watts R (2009) fMRI correlates of behavioural microsleeps during a continuous visuomotor task. Conf Proc IEEE Eng Med Biol Soc 2009:2919–2922

Rashbass C (1961) The relationship between saccadic and smooth tracking eye movements. J Physiol 159:326–338

Rothenberg S, Schottenfeld S, Selkoe D, Gross K (1980) Specific oculomotor deficit after acute methadone. II. Smooth pursuit eye movements. Psychopharmacology 67:229–234

Rowland LM, Thomas ML, Thorne DR, Sing HC et al (2005) Oculomotor responses during partial and total sleep deprivation. Aviat Space Environ Med 76:C104–C113

Russo M, Thomas M, Thorne D, Sing H et al (2003) Oculomotor impairment during chronic partial sleep deprivation. Clin Neurophysiol 114:723–736

Schluppeck D, Glimcher P, Heeger DJ (2005) Topographic organization for delayed saccades in human posterior parietal cortex. J Neurophysiol 94:1372–1384

Silver MA, Ress D, Heeger DJ (2005) Topographic maps of visual spatial attention in human parietal cortex. J Neurophysiol 94:1358–1371

Spering M, Carrasco M (2012) Similar effects of feature-based attention on motion perception and pursuit eye movements at different levels of awareness. J Neurosci 32:7594–7601

Stark L, Vossius G, Young LR (1962) Predictive control of eye tracking movements. IRE Trans Hum Factors Electron 2:52–57

Tanaka M (2005) Involvement of the central thalamus in the control of smooth pursuit eye movements. J Neurosci 25:5866–5876

Tavassoli A, Ringach DL (2009) Dynamics of smooth pursuit maintenance. J Neurophysiol 102:110–118

Thomas M, Sing H, Belenky G, Holcomb H et al (2000) Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 hours of sleep deprivation on waking human regional brain activity. J Sleep Res 9:335–352

Tomasi D, Wang RL, Telang F, Boronikolas V et al (2009) Impairment of attentional networks after 1 night of sleep deprivation. Cereb Cortex 19:233–240

Van Gelder P, Lebedev S, Liu PM, Tsui WH (1995) Anticipatory saccades in smooth pursuit: task effects and pursuit vector after saccades. Vision Res 35:667–678

Wang P, Nikolić D (2011) An LCD monitor with sufficiently precise timing for research in vision. Front Hum Neurosci 5:85

Westheimer G (1954) Eye movement responses to a horizontally moving visual stimulus. AMA Arch Ophthalmol 52:932–941

Wu JC, Gillin JC, Buchsbaum MS, Chen P et al (2006) Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. Neuropsychopharmacology 31:2783–2792

Yoshida A, Tanaka M (2009) Neuronal activity in the primate globus pallidus during smooth pursuit eye movements. NeuroReport 20:121–125

Zils E, Sprenger A, Heide W, Born J, Gais S (2005) Differential effects of sleep deprivation on saccadic eye movements. Sleep 28:1109–1115